

Nervous System and Endocrine System

- The Nervous System and the Endocrine System Coordinate Functions of the Body Systems
 - The nervous system controls homeostasis through nerve impulses that trigger the release of neurotransmitters whose effect results in either the excitation or inhibition of other neurons, muscle fibers, or gland cells.
 - The endocrine system releases hormones into the bloodstream which travels to the target organ where it alters the physiological activity of the cells.

Exhibit 13.1

Comparison of Nervous System and Endocrine System Regulation of Homeostasis

CHARACTERISTIC	NERVOUS SYSTEM	ENDOCRINE SYSTEM
Mechanism of control	Neurotransmitters released in response to nerve impulses.	Hormones delivered to tissues throughout the body by the blood.
Cells affected	Muscle cells, gland cells, other neurons.	Virtually all body cells.
Type of action that results	Muscular contraction or glandular secretion.	Changes in metabolic activities.
Time to onset of action	Typically within milliseconds.	Seconds to hours or days.
Duration of action	Generally briefer.	Generally longer.

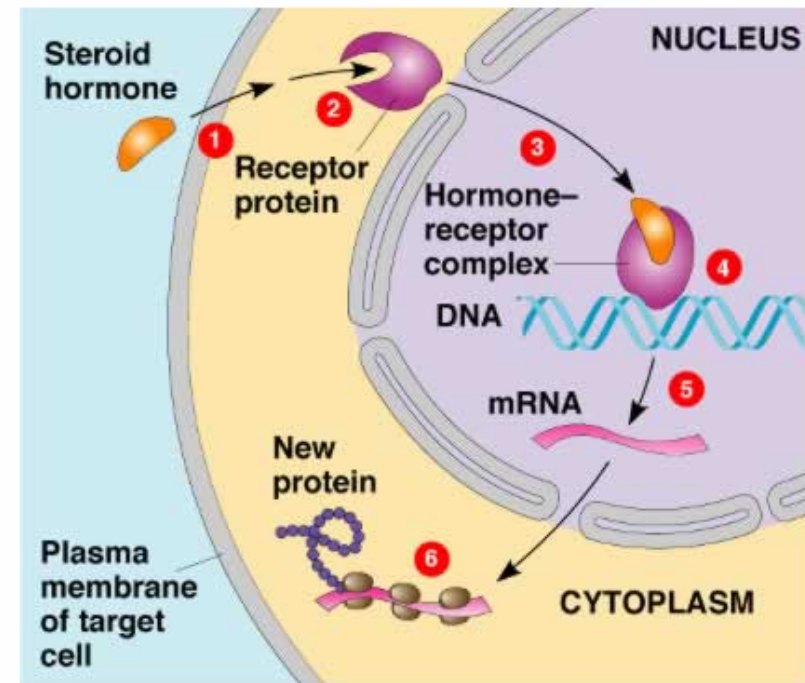
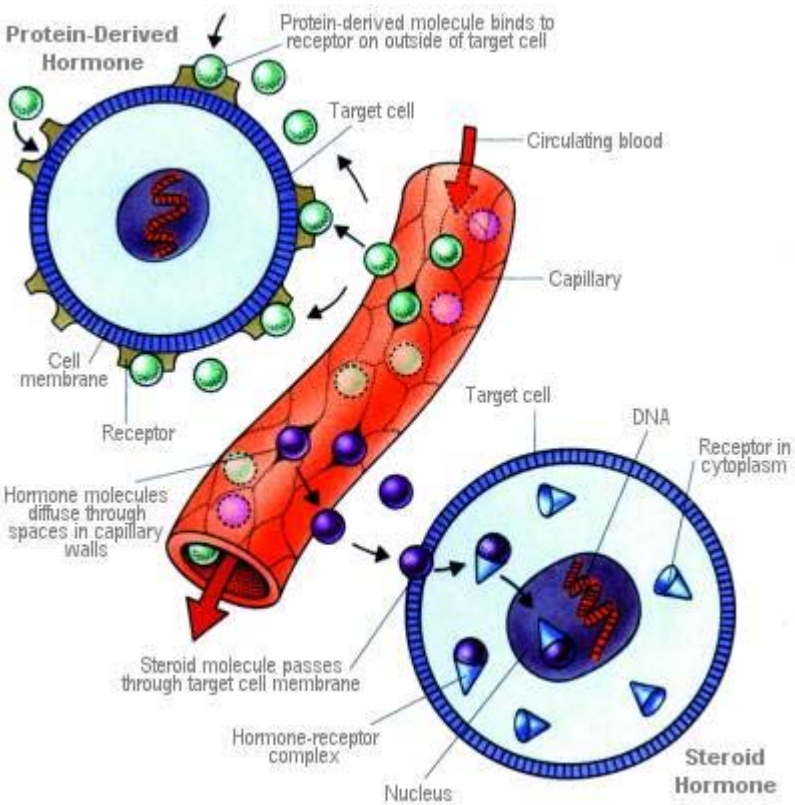
There are three general classes of hormones

Lipid soluble derivatives


- steroids- derived from cholesterol and are synthesized in the smooth ER
 - sex hormones- estrogen, progesterone, testosterone
- eicosanoids- derived from fatty acids
 - leukotrienes- has mostly local action and is involved in tissue inflammation
 - prostaglandins- has local action and is involved in inflammation, smooth muscle contraction, blood flow, intensify pain, and promote fever. (Aspirin and ibuprofen [Motrin] inhibit prostaglandin synthesis.)

Water soluble derivatives

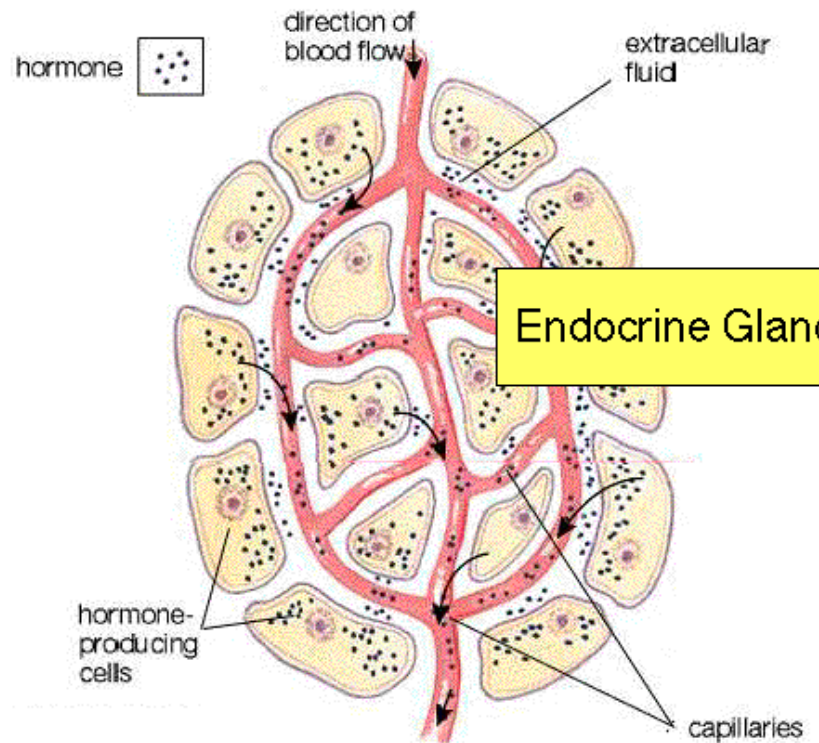
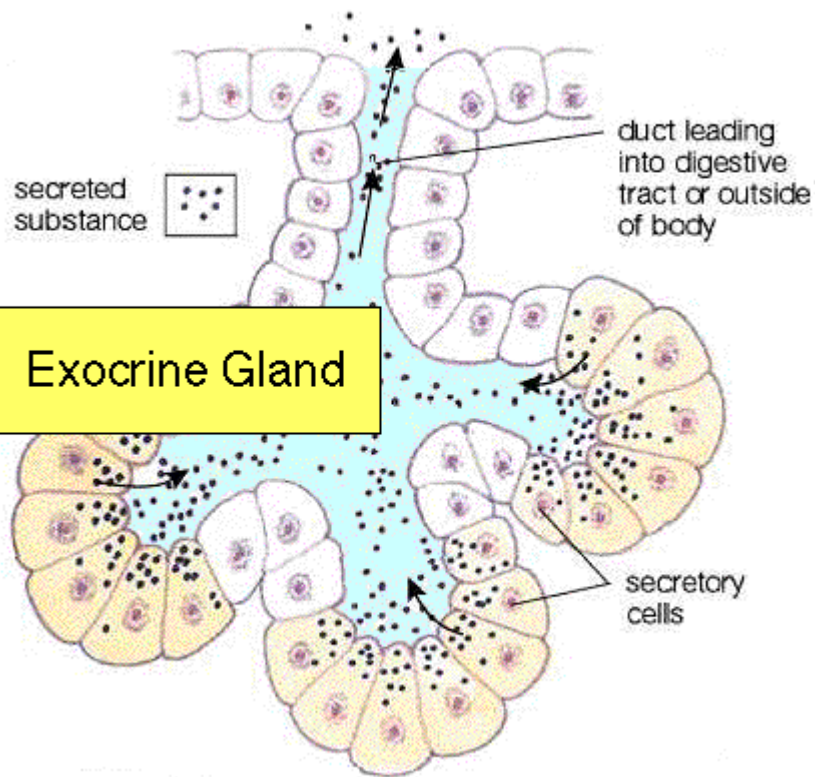
- Amino acid derivatives
- Peptide and Proteins



Endocrine Glands

- The body has two types of glands
 - Exocrine glands- secrete their products into ducts that carry the secretions into body cavities or on to body surfaces.
 - Sweat glands (sudoriferous glands)
 - oily glands (sebaceous glands)
 - mucous glands
 - digestive glands
 - Endocrine glands- ductless glands that secrete their products (hormones) into the extracellular space around the secretory cells (local action) which then diffuse into the blood vessels (distant action)

Endocrine gland picture



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Endocrine System

Endocrine glands of the body that constitute the endocrine system

- Pituitary gland
- Thyroid
- Parathyroid
- Adrenal
- Pineal

Tissues that contain cell that secrete hormones but not considered endocrine glands exclusively

- Hypothalamus
- Thymus
- Pancreas
- Ovaries
- Testes
- kidneys
- Stomach
- Liver
- Small intestine
- Skin
- Heart
- Adipose tissue
- placenta

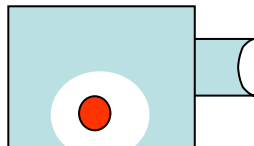
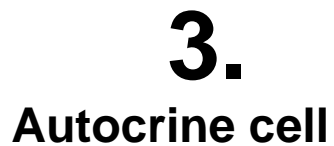
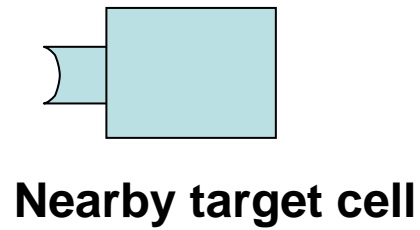
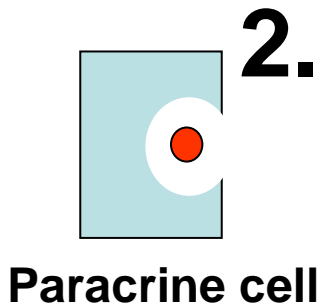
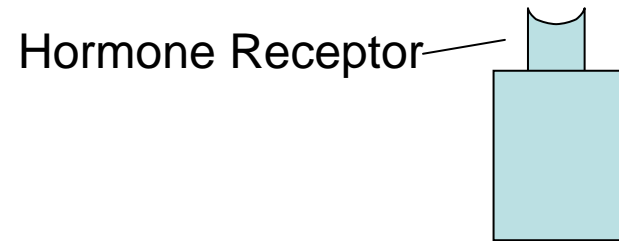
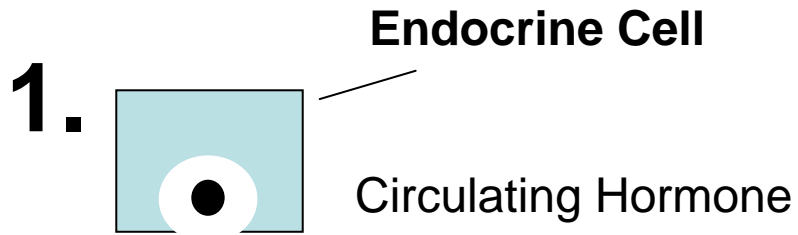
Circulating and Local Hormones

Circulating hormones- hormones that pass into the blood stream and act on distant target cells.

- Linger in the blood and exert their effects for a few minutes or a few hours
 - Are inactivated by the liver and excreted by the kidney

Local hormones- those that act locally without first entering the bloodstream.

- Paracrines- hormones that act on neighboring cells
- Autocrines- those that act on the same cell that secreted them.
- Are usually inactivated quickly
- Ex: nitric oxide (NO)- released by endothelial cell which causes relaxation of nearby vascular smooth muscle, in turn causing vasodilation and increased blood flow



Chemical Classes of Hormones

Water –soluble Hormones

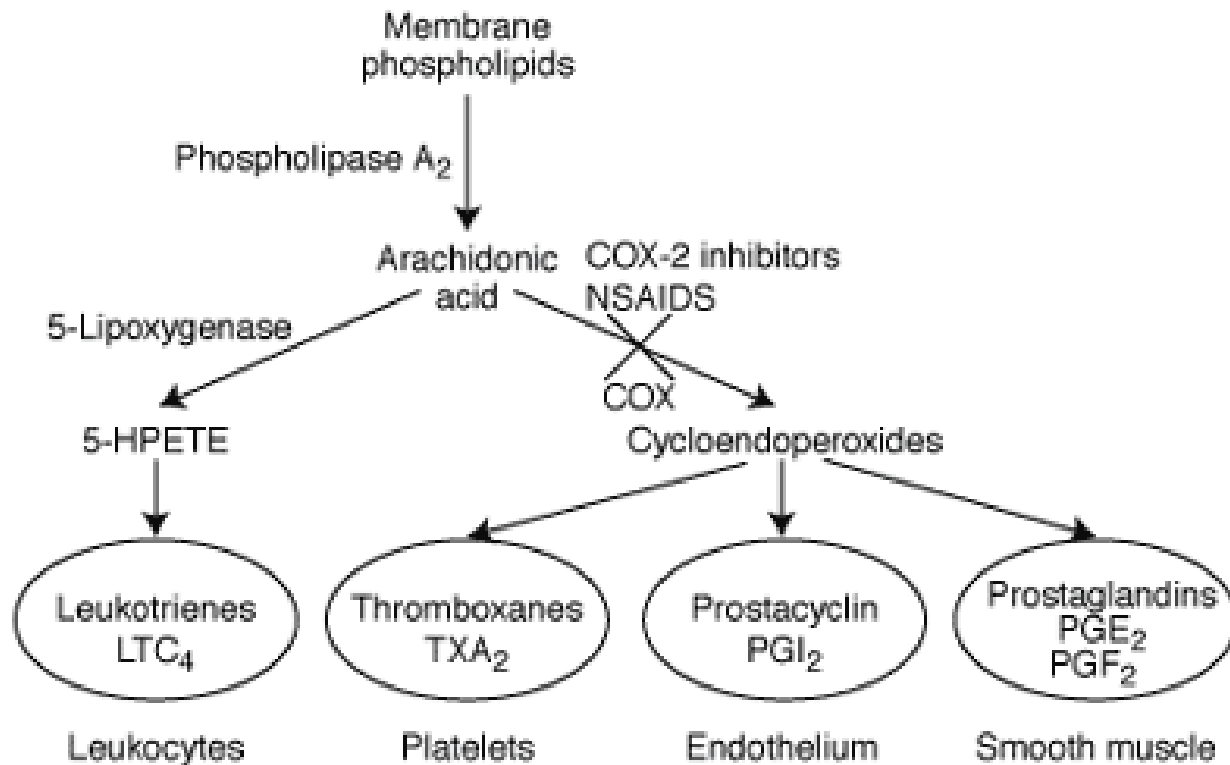
- Monoamine (biogenic amines) hormones- synthesized by modifying certain amino acids
 - Catecholamines- (made from tyrosine) epinephrine, norepinephrine, and dopamine
 - Histamine- from histidine by mast cells and platelets
 - Serotonin and melatonin- from tryptophan
- Peptide and protein hormones- synthesized on the rough ER and consist of chains 3-200 amino acids
 - Ex: Thyroid-stimulating hormone (TSH)

Chemical Classes of Hormones

- Eicosanoid hormones- chemical mediators derived from arachidonic acid (a 20-carbon fatty acid) located in the phospholipids in the plasma membrane
- leukotrienes- mediates allergic reactions
 - derived from the enzyme **lipoxigenase** action on arachidonic acid

cyclooxygenase converts arachidonic acid to three other types of eicosanoids

- Prostacyclin- produced by the walls of blood vessels, where it inhibits blood clotting and vasoconstriction
- Thromboxanes- produced by blood platelets
 - in the event of injury, they override prostacyclin and stimulate vasoconstriction and clotting
- Prostaglandins- are the most diverse eicosanoid
 - thought to be produced in most organs of the body
 - promotes fever and pain in inflammation
 - has differing other effects, depending on the organ



- Non steroidal anti-inflammatory drugs stop the action of cyclooxygenase, thus blocking prostaglandin synthesis thereby reducing
 - fever and pain in inflammation (decreased prostaglandin)
 - decrease blood clotting (decreased production of prostacyclin)

Hormone Transport in the Blood

- Most water soluble hormone molecules circulate in the blood in the free form (not attached to a protein)
- Most lipid soluble hormones bind to transport proteins
- **Transport proteins** are albumin and globulins synthesized by the liver and have three functions
 - Improve the transportability of the lipid-soluble hormones by making them temporarily water-soluble
 - Retard passage of the small hormone molecules through the filtering mechanism in the kidneys, thus slowing the rate of hormone loss in the urine
 - Provide a ready reserve of hormone, already present in the bloodstream

- they protect circulating hormones from being broken down by enzymes in the blood plasma and liver
 - free hormones may be broken down or cleared from the blood in minutes, whereas bound hormones may circulate for hours or weeks.

Hormone Transport

- Bound hormone- hormones attached to a transport protein
- Unbounded (free) hormone- one that is not attached to a transport protein
- Only the free hormone can leave a blood capillary and get to a target cell.

Hormone Transport in the Blood

- Up to 10% of the molecules of a lipid hormone are not bound to a transport protein, i.e. free fraction
- It is the free fraction that diffuses out to capillaries, binds to receptors, and triggers responses.
- Transport proteins release new ones to replenish the free fraction

Example of transport proteins

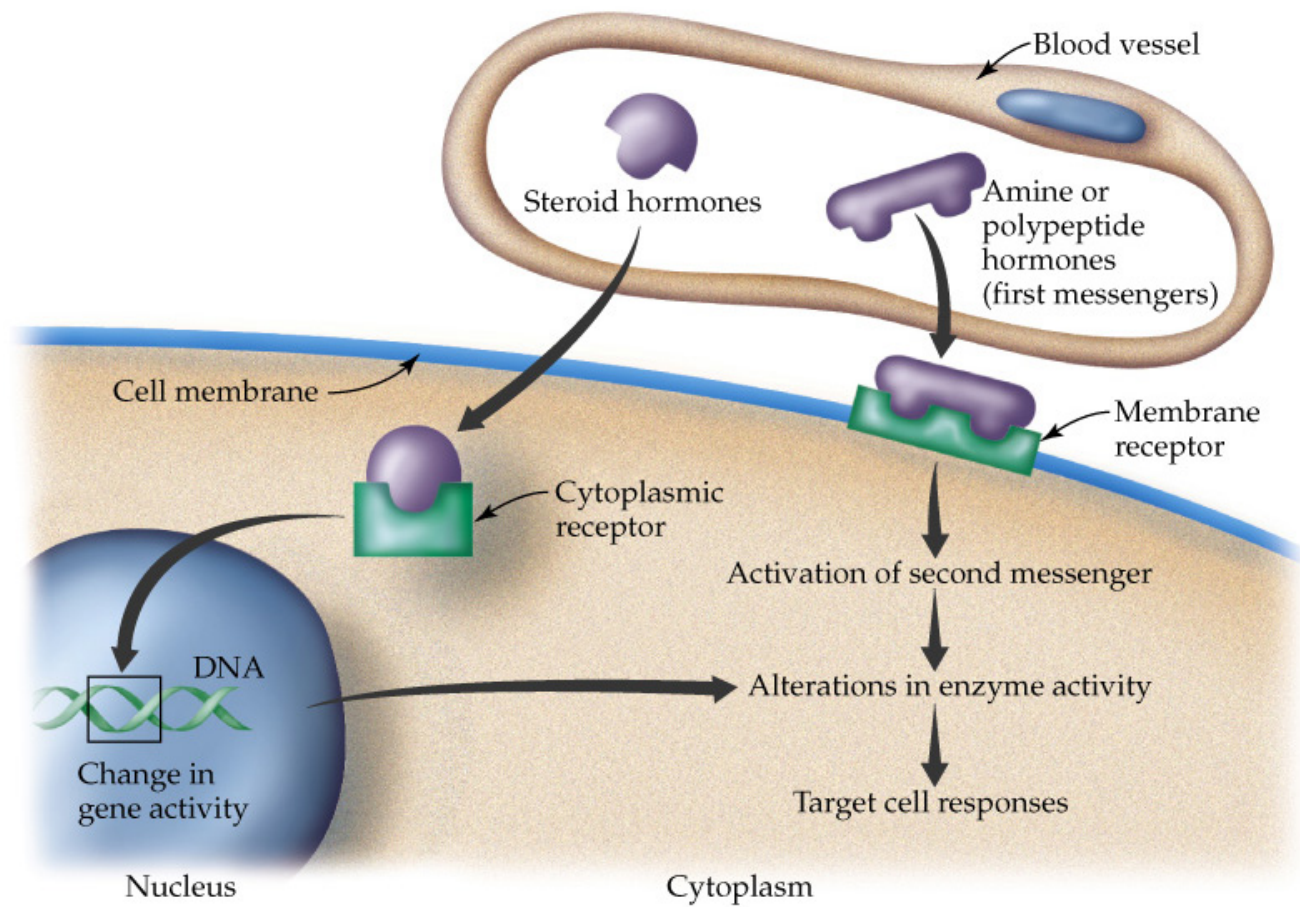
- Thyroid hormone binds to three transport proteins
 - albumin
 - albumin-like protein called thyretin
 - an alpha globulin named thyroxine binding globulin (TBG)
 - binds most of the greatest amount
 - 99.8% of T3 and T4 are protein bound
 - bound TH serves as a long-lasting blood reservoir
- Steroid hormones bind to globulins such as transcortin, the transport protein for cortisol.

Mechanisms of Hormone Action

- Hormone response depends on both the hormone and the target cell
- Hormone may elicit different responses in different target cells
 - Ex: insulin stimulates glycogen synthesis in the liver and triglyceride synthesis in fat cells
- Depending on whether a hormone is lipid-soluble or water-soluble, its target cell receptors may be either inside the cell or in the plasma membrane
- Hormone responses may include
 - Synthesis of new molecules
 - Changing the permeability of the plasma membrane
 - Stimulating the transport of substances into or out of the cell
 - Altering the rate of specific metabolic reactions
 - Causing contraction of smooth or cardiac muscle

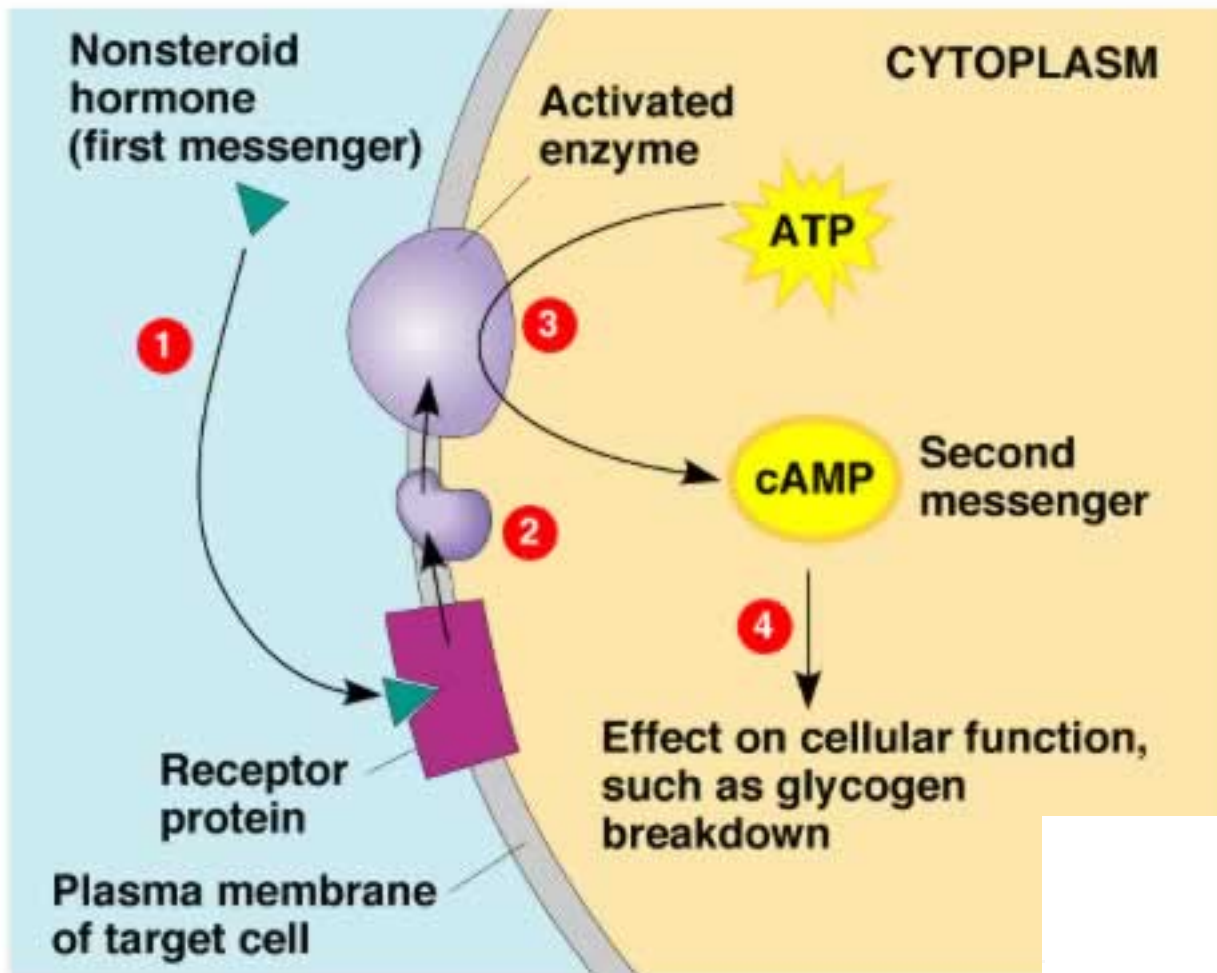
Action of Lipid-soluble Hormones

- Diffuses through the lipid bilayer of the plasma membrane
- Will bind to and activate receptors located within the cytosol or nucleus
- Activated receptor then alters gene expression by turning on or off specific genes in the DNA
- New messenger RNA is transcribed from which new protein are synthesized at the ribosomes
- The new proteins alter the cell's activity and cause the typical physiological responses of that hormone

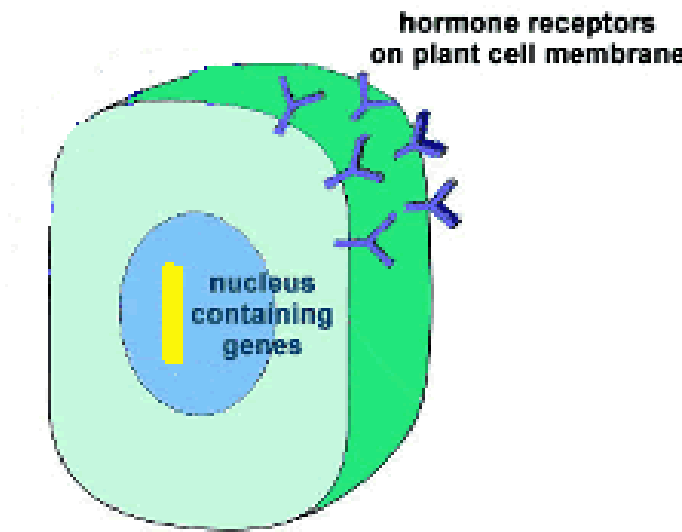


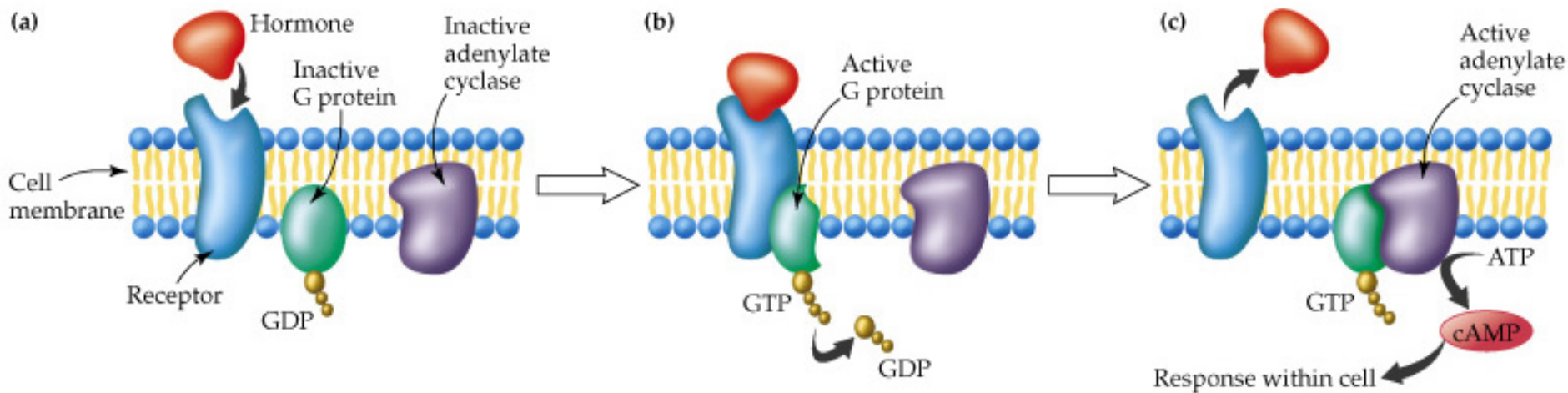
Action of Water-soluble Hormone

- Binds at the membrane receptor (first messenger)
- A second messenger is released within the cell where hormone-stimulated responses can take place
- One common second messenger is **cylic AMP** (cAMP), which is synthesized from ATP
- G-protein- link receptors on the outer surface of the membrane to the adenylate cyclase on the inner surface
 - The binding of a hormone to its receptor activates many G-protein molecules, which in turn activate molecules of adenylate cyclase.
 - Unless activated by more hormone, G-protein slowly deactivates, thus stopping hormone response



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Clinical Application

Cholera Toxin and G Protein

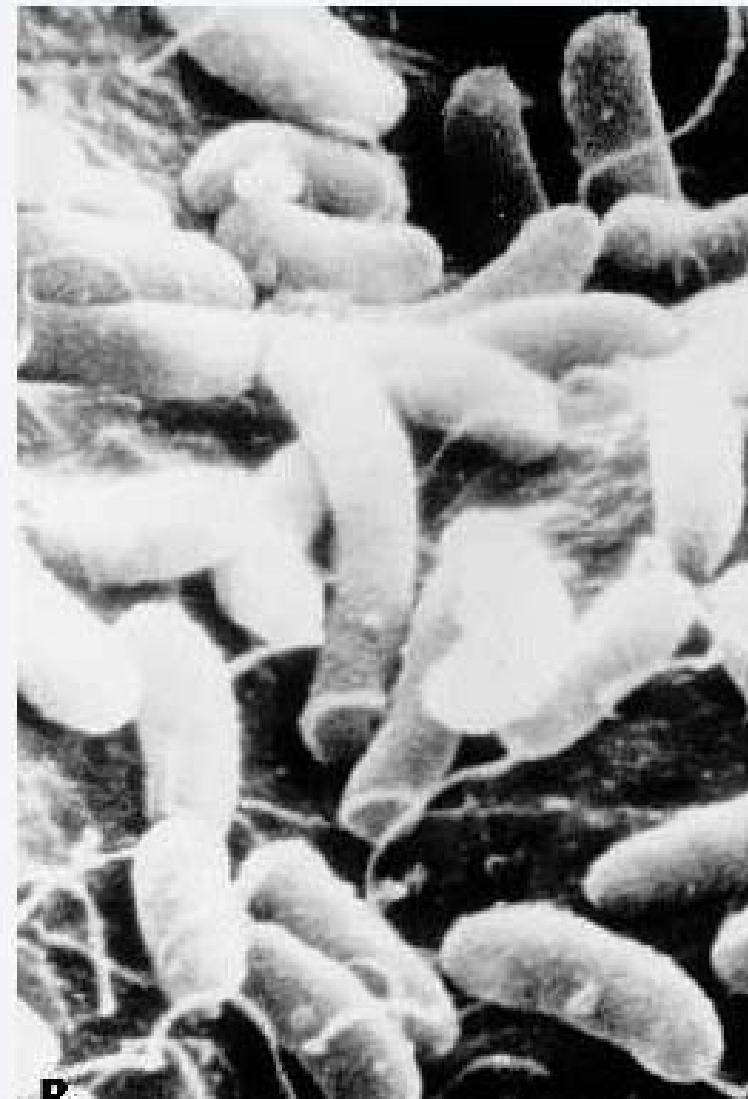
- Cholera toxin produces massive watery diarrhea in which a person can rapidly die of dehydration
- Toxin modifies G protein in the intestinal epithelial cells such that they become locked in an activated state.
 - Results in large intracellular concentration of cAMP
 - Effect is to stimulate an active transport pump that ejects chloride ions from the cells into the lumen followed by water (osmosis) and sodium ions
 - Treatment consist of replacement of lost fluids, either intravenously or by mouth, plus antibiotics (tetracycline)

Vibrio cholerae: Colonization

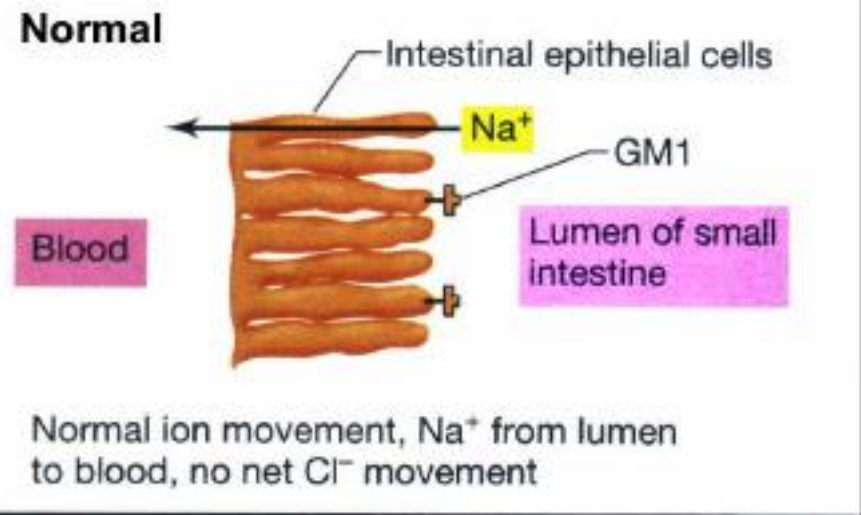
Vibrio cholerae attachment and colonization in experimental rabbits. TEM and SEM during early infection .



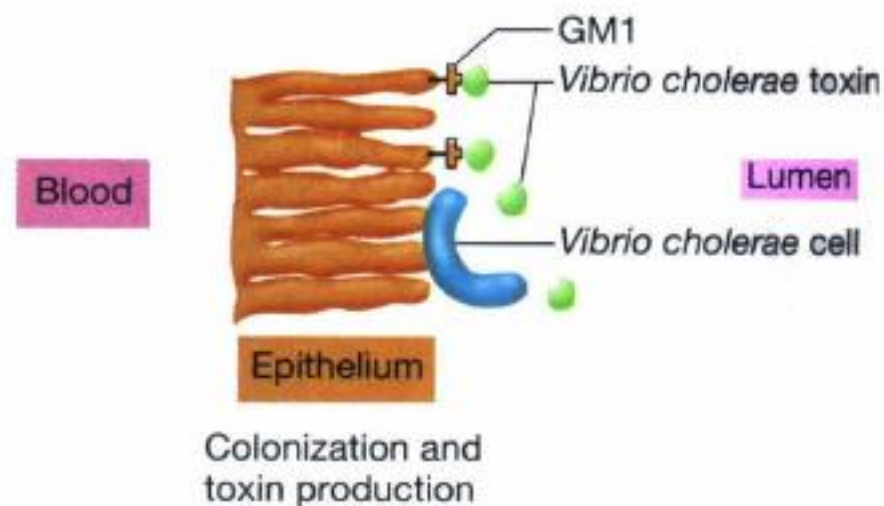
(From Nelson, ET et al.: Infect Immun 14:527, 1976)



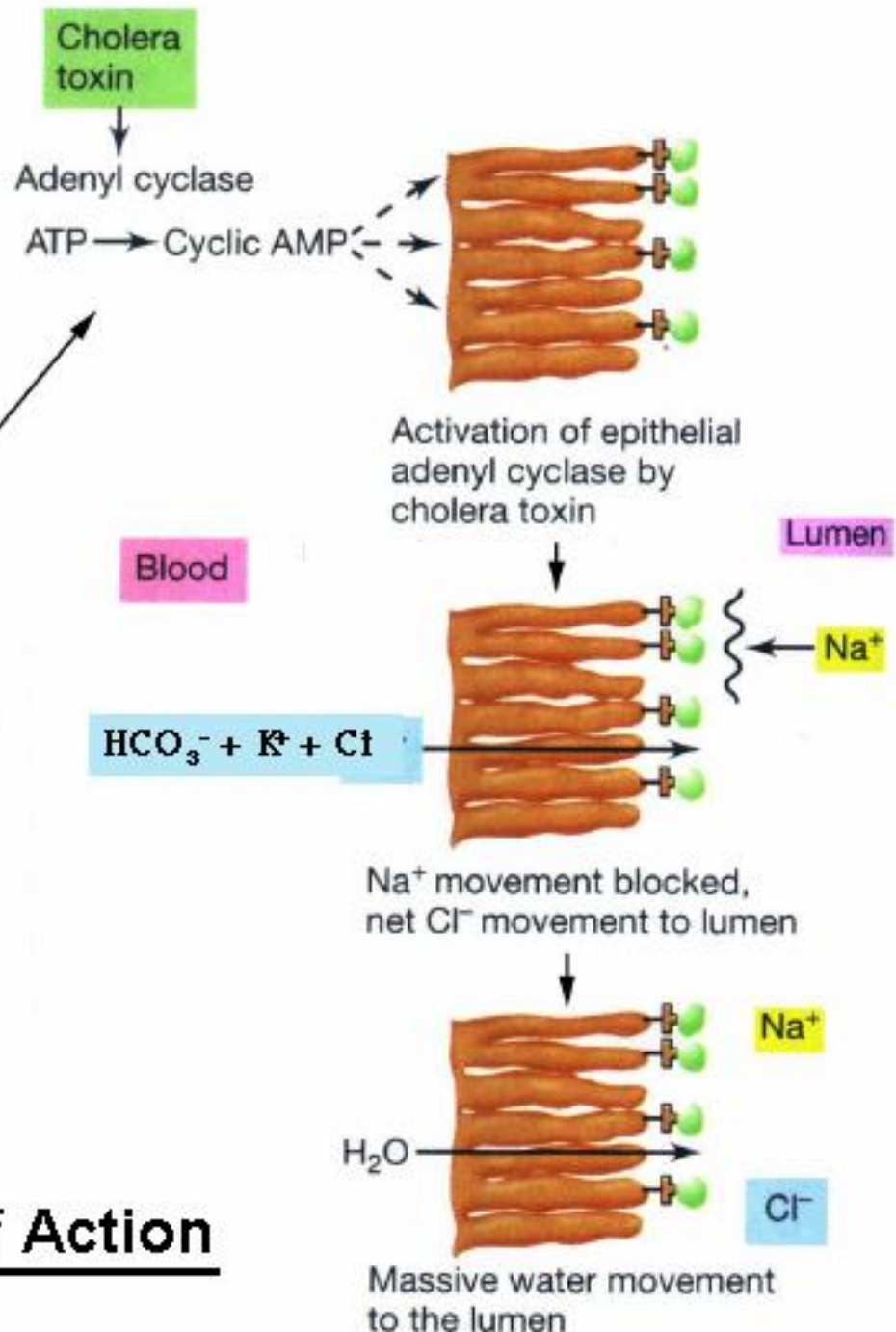
Normal



V. cholerae infected



Cholera Toxin, Mechanism of Action



Hormone Interactions

- Responsiveness to a target cell to a hormone depends on
 - The hormone concentration
 - The abundance of the target cell's hormone receptors
 - Influences exerted by other hormones
- **Permissive effect-** when the actions of a hormone on target cells require a simultaneous or recent exposure to a second hormone.
 - Ex: Epinephrine alone only weakly stimulates lipolysis, but when small amounts of thyroid hormones are also present, the same amount of epinephrine stimulates lipolysis much more powerfully

Hormone Interactions

- **Synergistic effects-** when the effect of two hormones acting together is greater or more extensive than the sum of each hormone acting alone
- **Antagonistic effects-** when one hormone opposes the activation of another hormone.
 - Ex: Insulin promotes glycogen synthesis by the liver cells and glucagon stimulates glycogen breakdown

Enzyme Amplification

- one hormone molecule does not trigger the synthesis of just one enzyme molecule
- It activates thousands of enzymes molecules through a cascade called **enzyme amplification**
- This enables a very small stimulus to produce a very large effect.
- Hormones are therefore needed in very small quantities
 - **their circulating concentrations are very low compared to other blood substances: on the order of nanograms per deciliter of blood**
- Because of amplification, target cells do not need a great number of hormone receptors

Hormone Clearance

- Hormone signals, like nervous signals, must be turned off when they have served their purpose
 - Most hormones are taken up and degraded by the liver and kidneys and then excreted in the bile or urine
 - Some are degraded by the target cells
- The rate of hormone removal is called the metabolic clearance rate (MCR)
- Half life- the length of time required to clear 50% of the hormone from the blood
 - the faster the MCR the shorter the half life

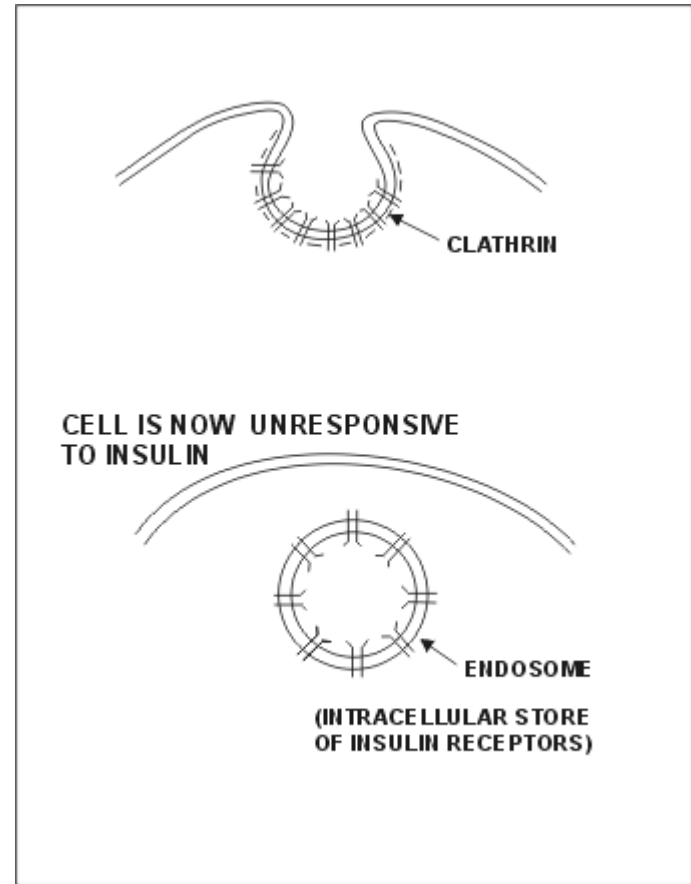
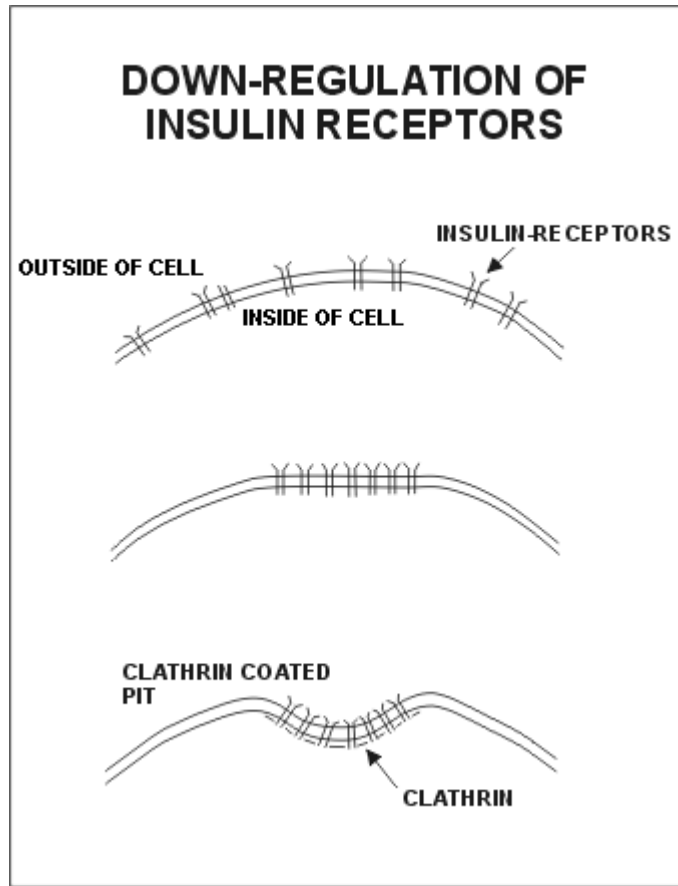
Modulation of Target Cell Sensitivity

- Hormones affect only target cells
 - Cells that carry specific receptors that bind the recognized hormone
- Down regulation- when receptor quantity decrease when hormone is in excess
 - Decreases responsiveness to hormone
- Up regulation- when receptor quantity increases when hormone is deficient
 - Makes target cell more sensitive to hormone

Down reg
slide

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Receptor Down Regulation

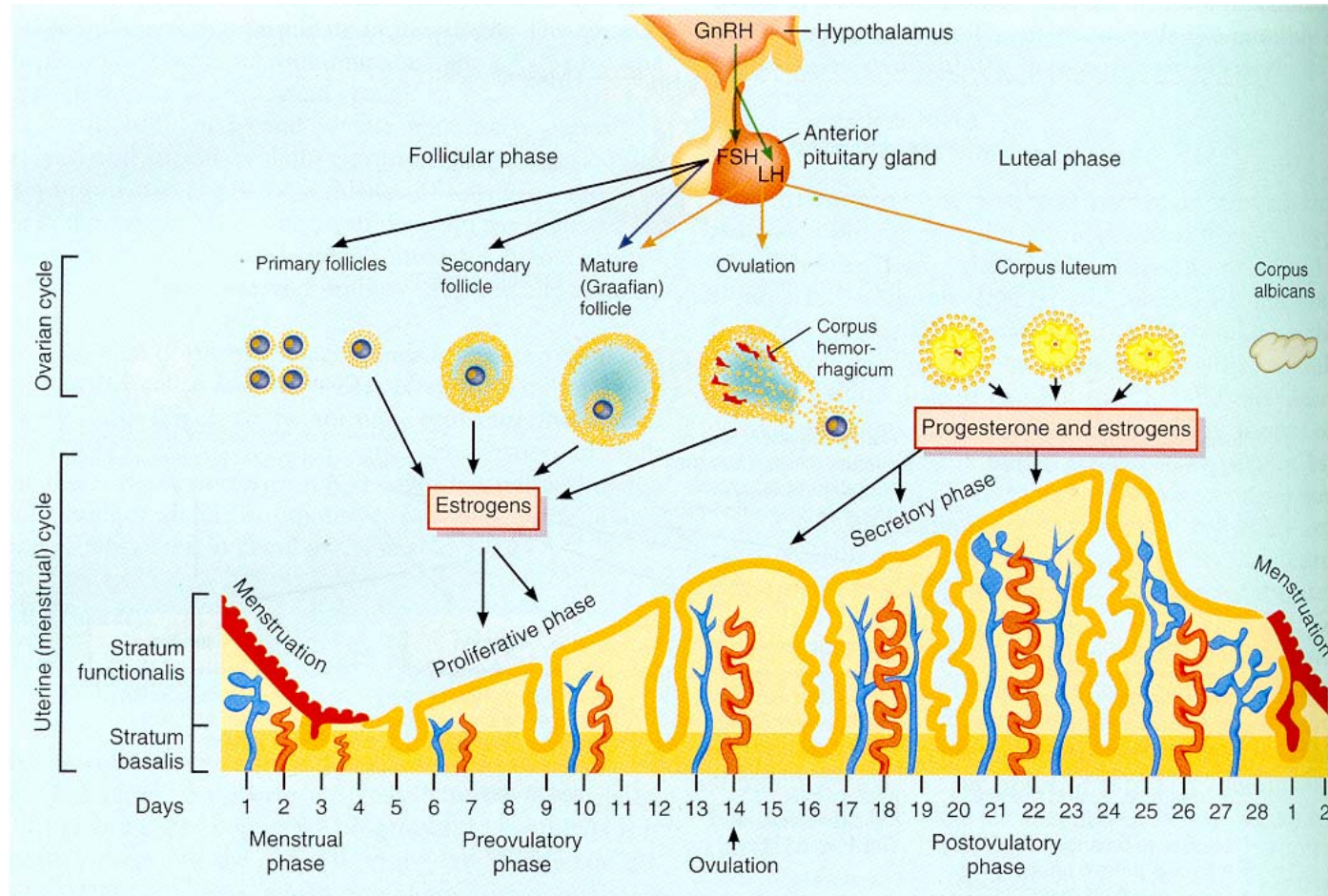


Clinical Application

Blocking Hormone Receptors With Abortion Pill

RU486 (mifepristone),
the abortion pill

- Blocks progesterone receptors in the endometrium, preventing endometrial growth.
- Endometrial sloughs off with embryo



Control of Hormone Secretion

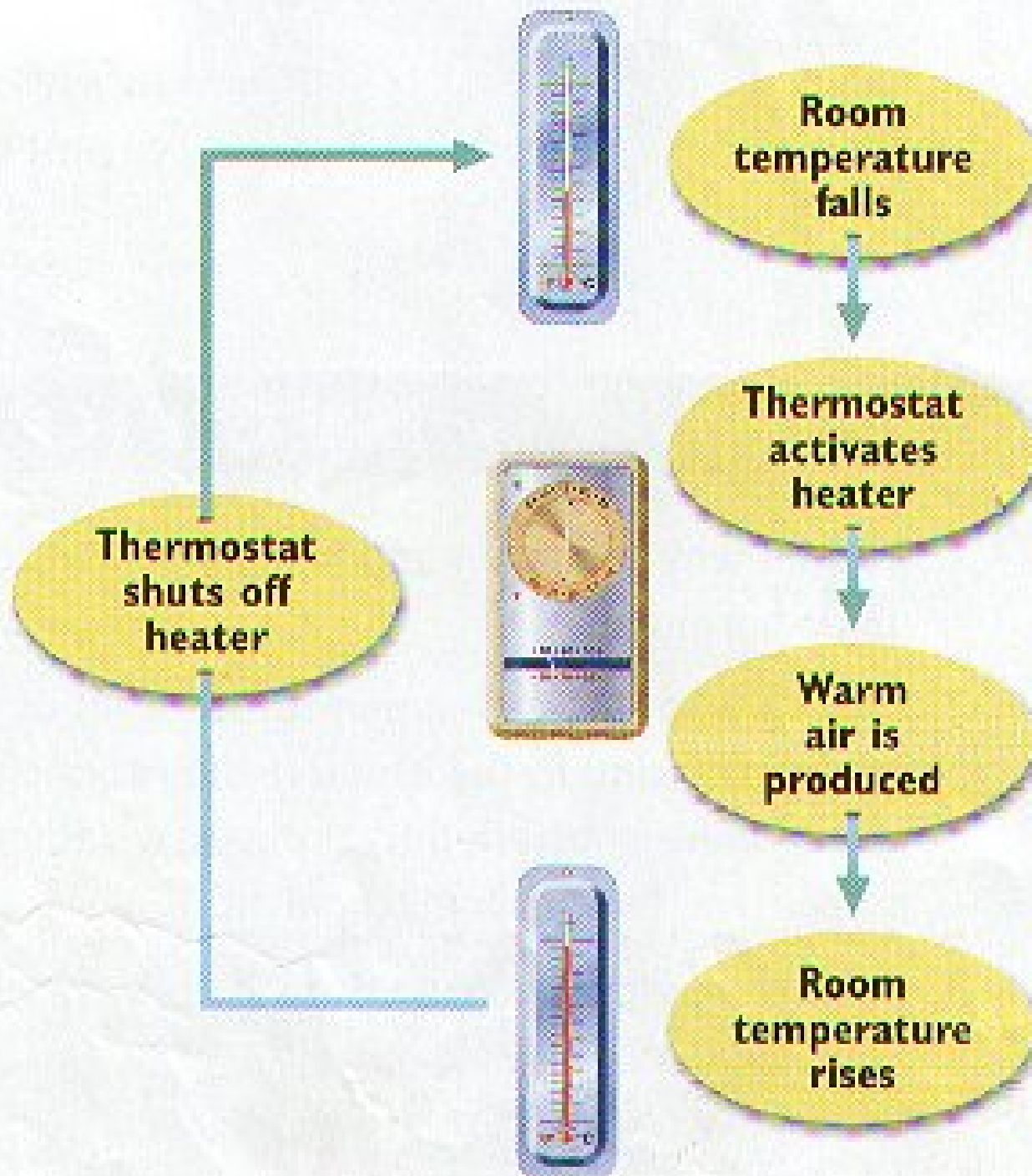
- Most hormones are released in short burst, with little or know secretion in between.
- Increased stimulation causes more frequent burst, thereby increasing blood concentration
- Hormone secretion is regulated by
 - Signals from the nervous system
 - Chemical changes in the blood
 - Other hormones
 - Ex: nerve impulses to the adrenal medulla regulate the release of epinephrine
 - Blood calcium regulates the release of parathyroid hormone
 - Adrenocorticotrophic hormone from the pituitary gland stimulates the release of cortisol by the adrenal cortex

Control of Hormone Secretion (cont)

Disorders of the endocrine system often involve either

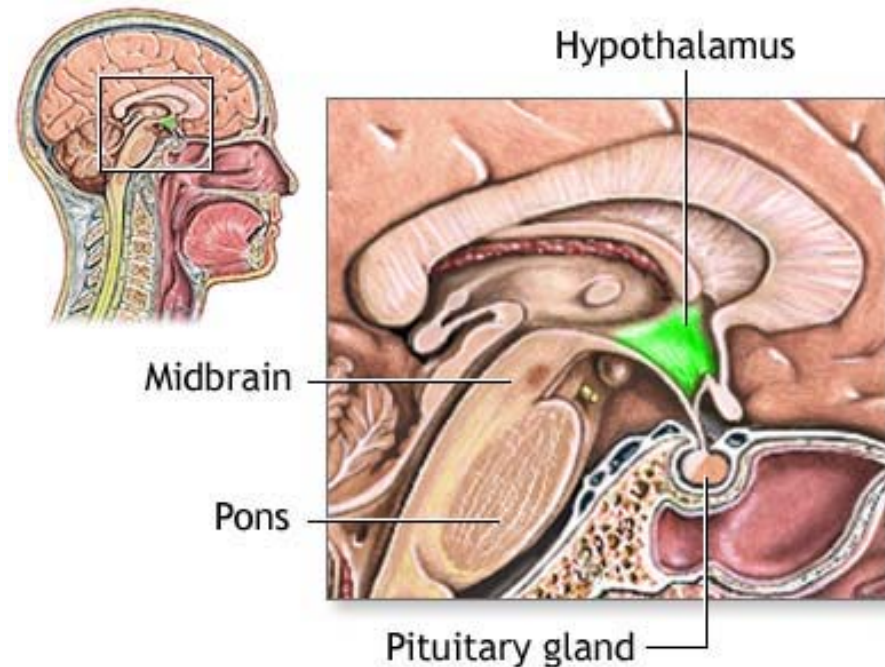
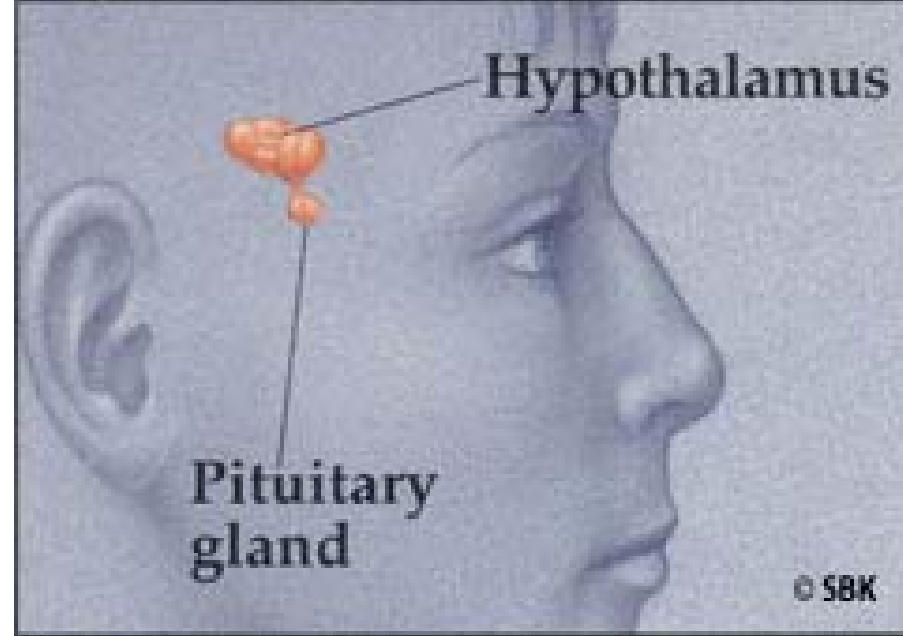
- Hyposecretion- inadequate release of hormone
- Hypersecretion- excessive release of hormone
- Most cases are due to
 - Faulty control of secretion
 - Faulty hormone receptors
 - Inadequate number of receptors
- Most hormonal regulatory systems work via negative feedback
- Occasionally a positive feedback system contributes of regulation
 - In child birth, where oxytocin stimulates contractions of the uterus and the uterus in turn stimulates more oxytocin release.

Negative feedback



Hypothalamus and Pituitary Gland

- Hypothalamus-
 - Controls the pituitary
 - The major integrating link between the nervous and endocrine system
 - Receives input from
 - several regions of the brain
 - Painful, stressful, and emotional experiences cause changes in hypothalamus activity
 - Sensory signals from internal organs
 - retina



Hypothalamus and Pituitary Gland (cont)

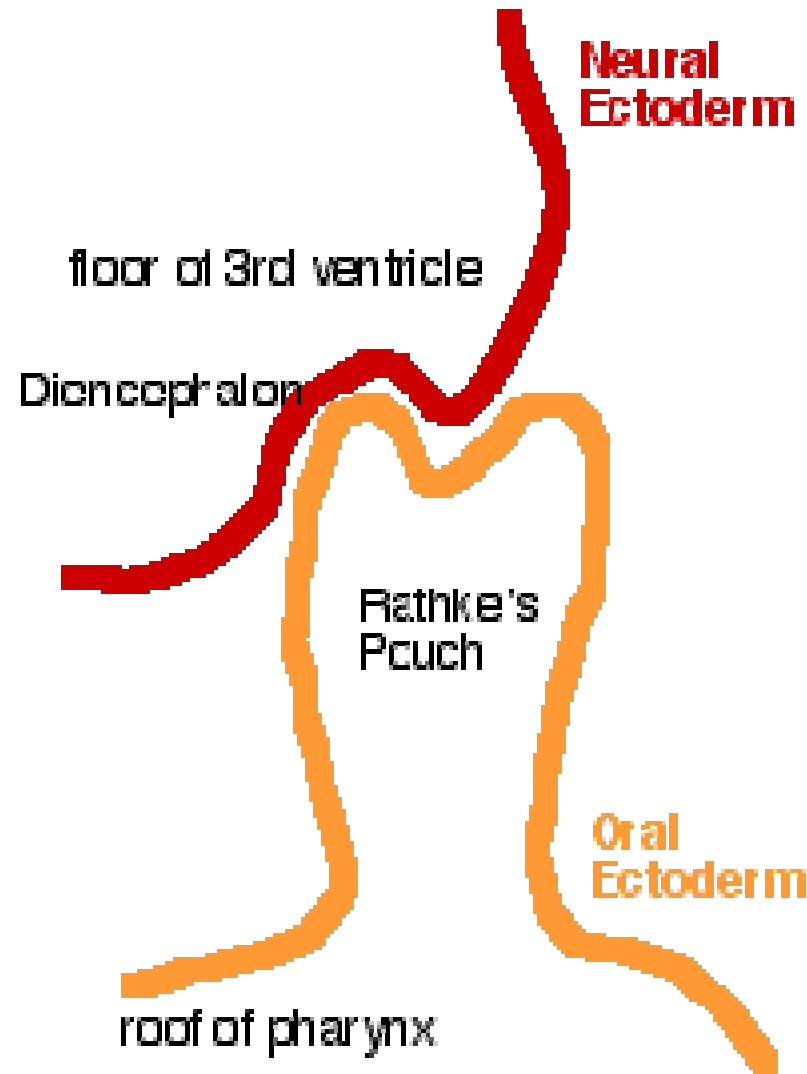
- Hypothalamus controls
 - Autonomic nervous system
 - Regulates body temperature
 - Thirst
 - Hunger
 - Sexual behavior
 - Defense reaction such as fear and rage
- Is a crucial endocrine gland
 - Synthesizes at least nine different hormones

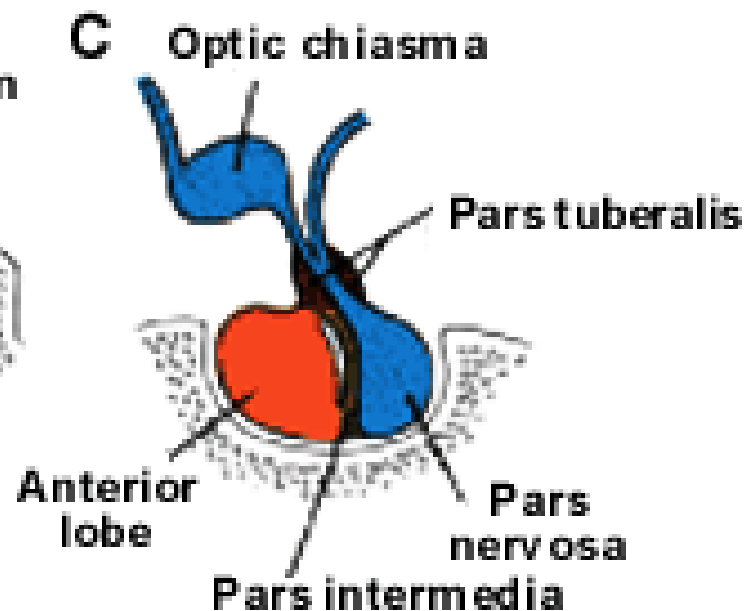
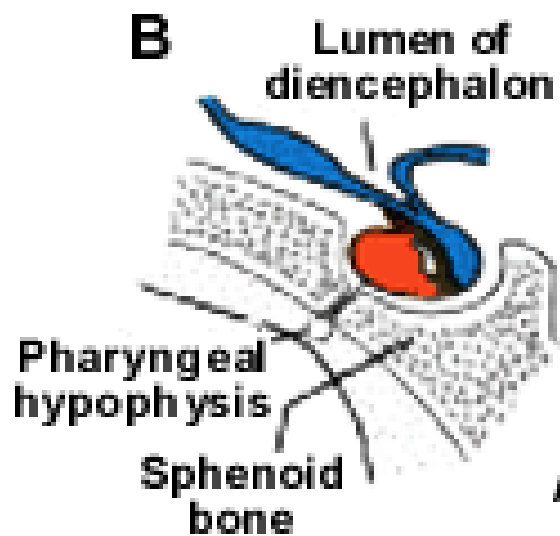
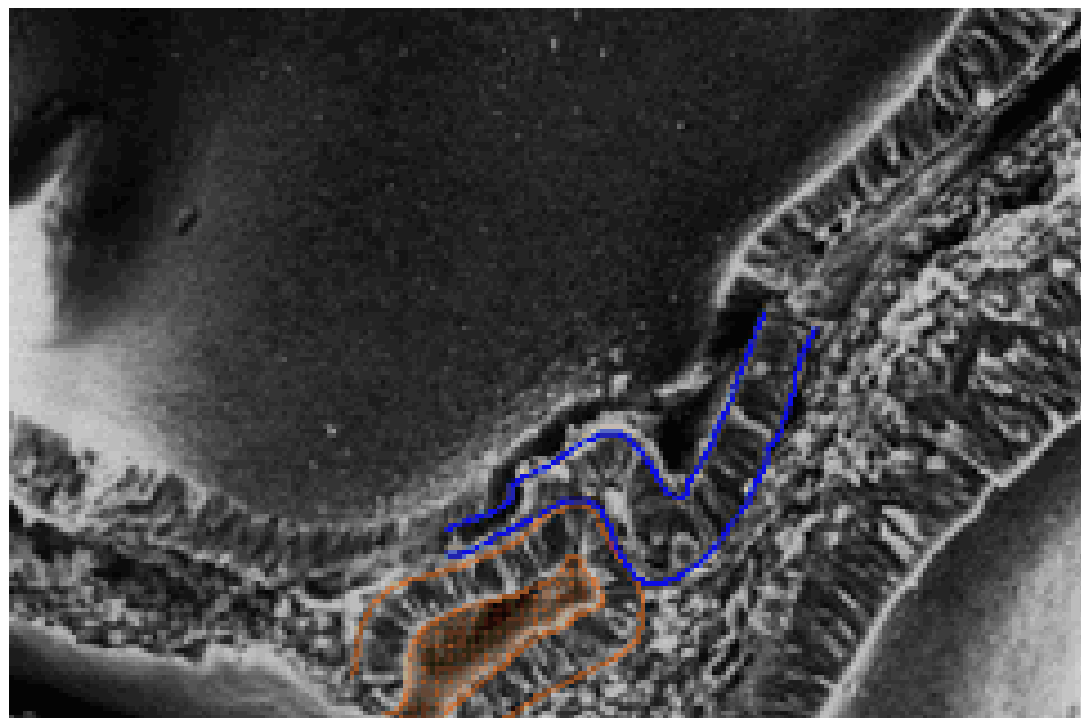
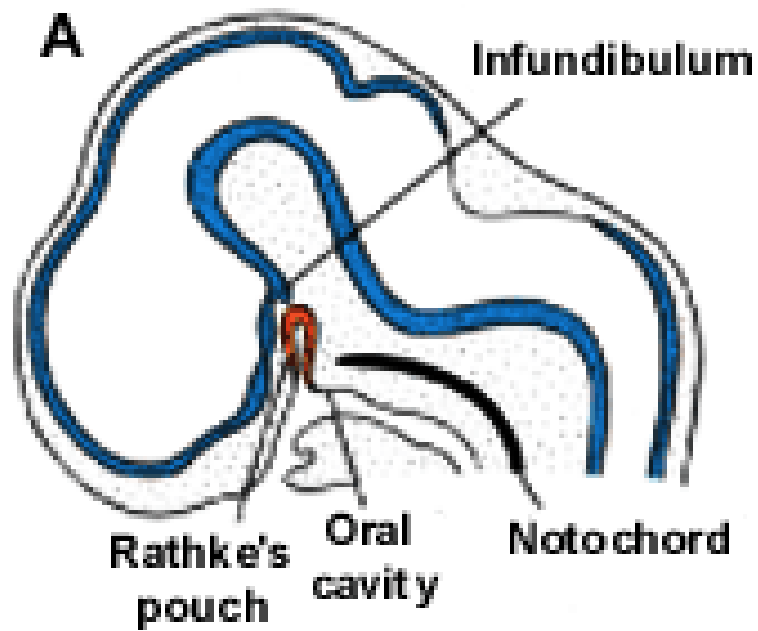
Hypothalamus and Pituitary Gland (cont)

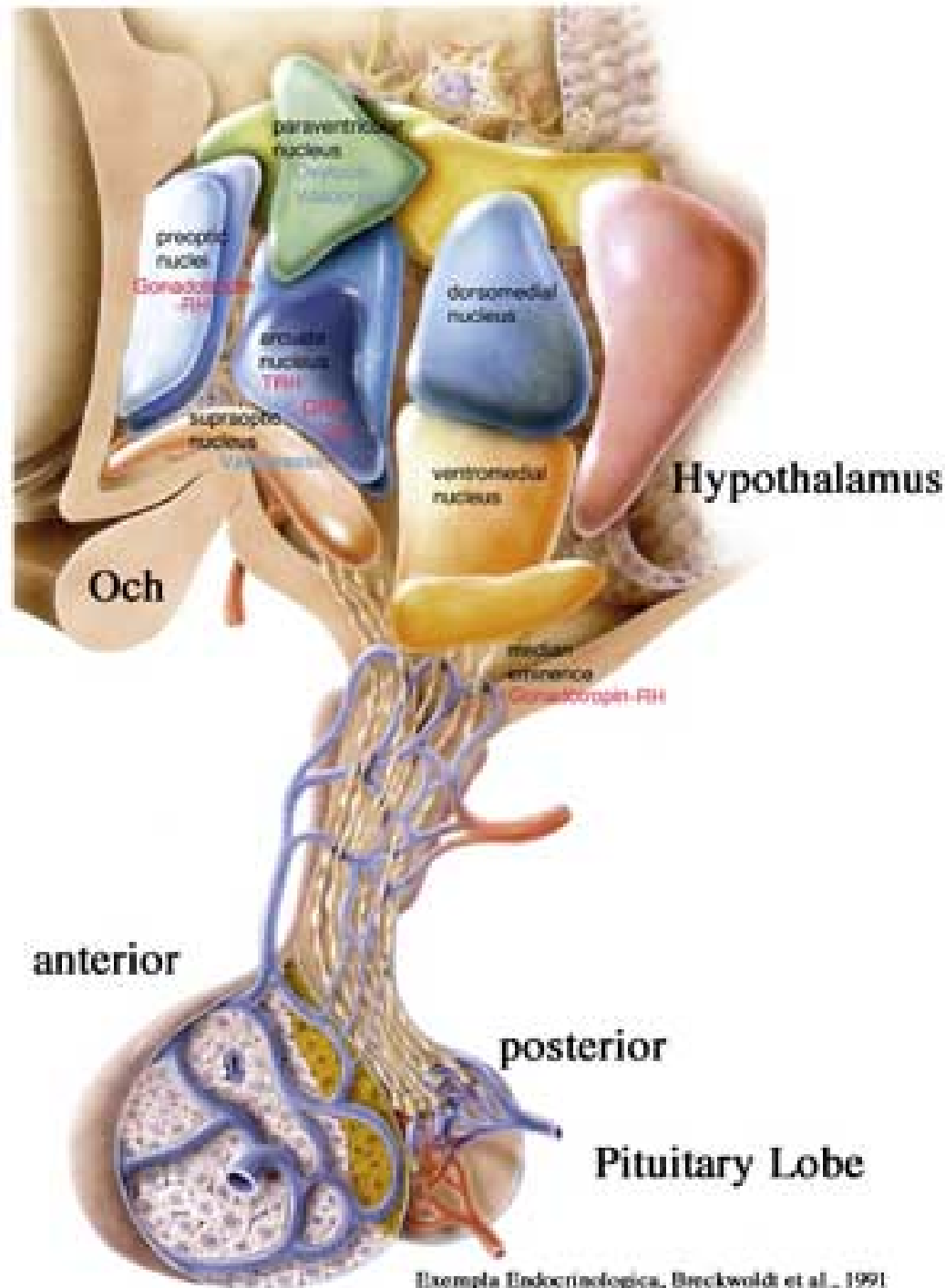
- Pituitary gland (hypophysis)
 - Pea shaped structure that lies in the sella turcica of the sphenoid bone
 - Attaches to the hypothalamus by a stalk called the **infundibulum**
 - Has two anatomical and functionally separate parts
 - Anterior pituitary (anterior lobe)- 70% of weight of gland
 - Posterior pituitary (posterior lobe)
 - Contains axons and axon terminals whose cell bodies are located in the hypothalamus
 - Pars intermedia- atrophies during fetal development
 - Ceases to exist as a separate lobe in adults

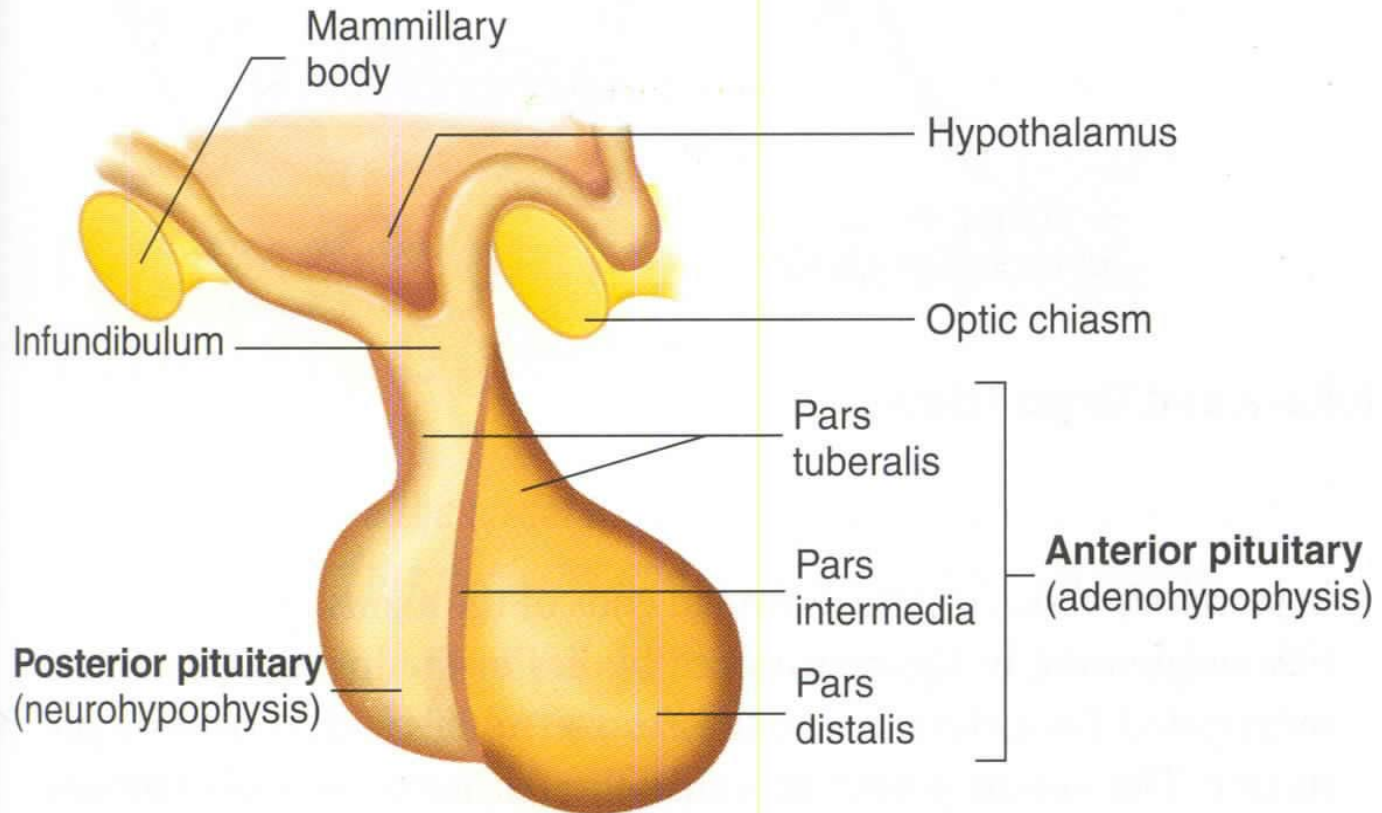
Pituitary Gland

- Arises from two embryologically separate structures
 - **adenohypophysis**-arises from a hypophyseal pouch that grows upward from the pharynx
 - **neurohypophysis**- arises as a downgrowth of the brain, the neurohypophyseal bud
- They come to lie side by side and are closely joined that they look like a single gland



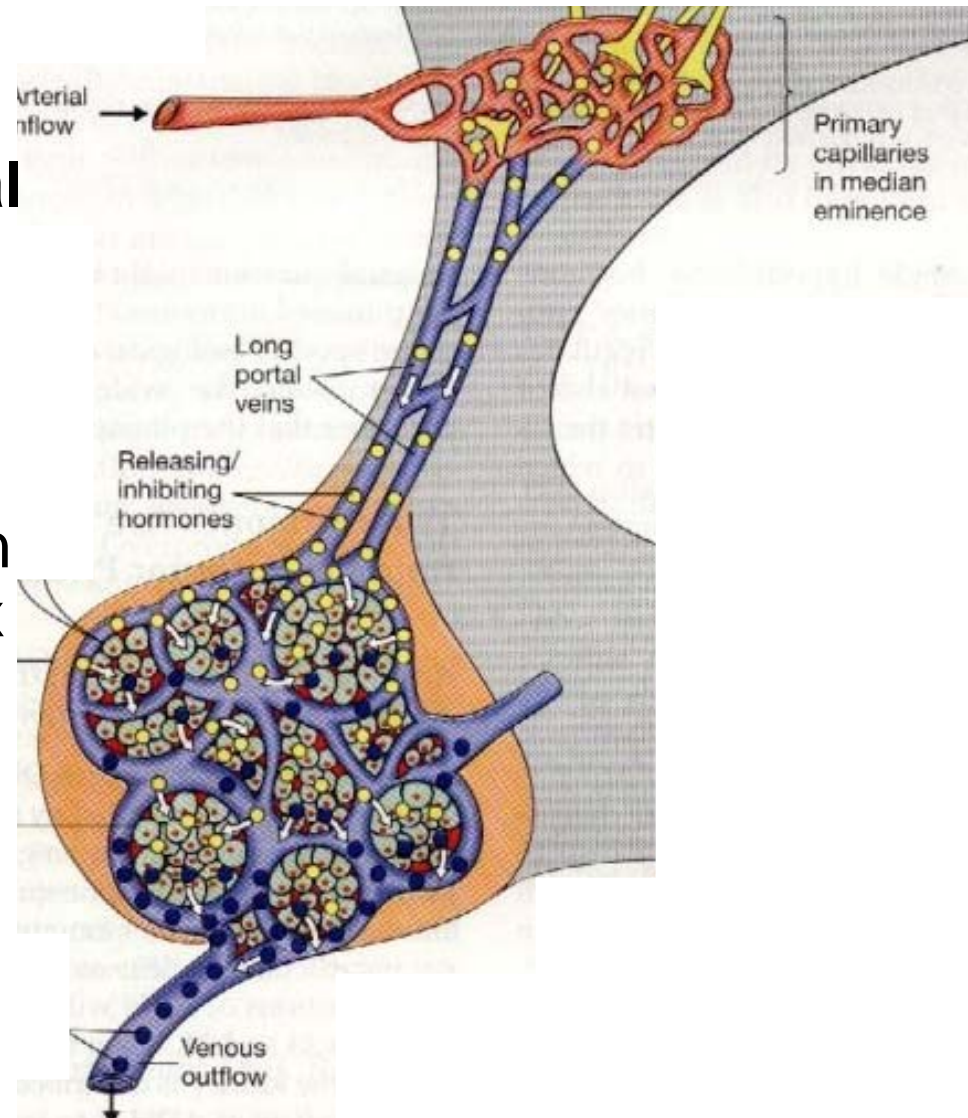




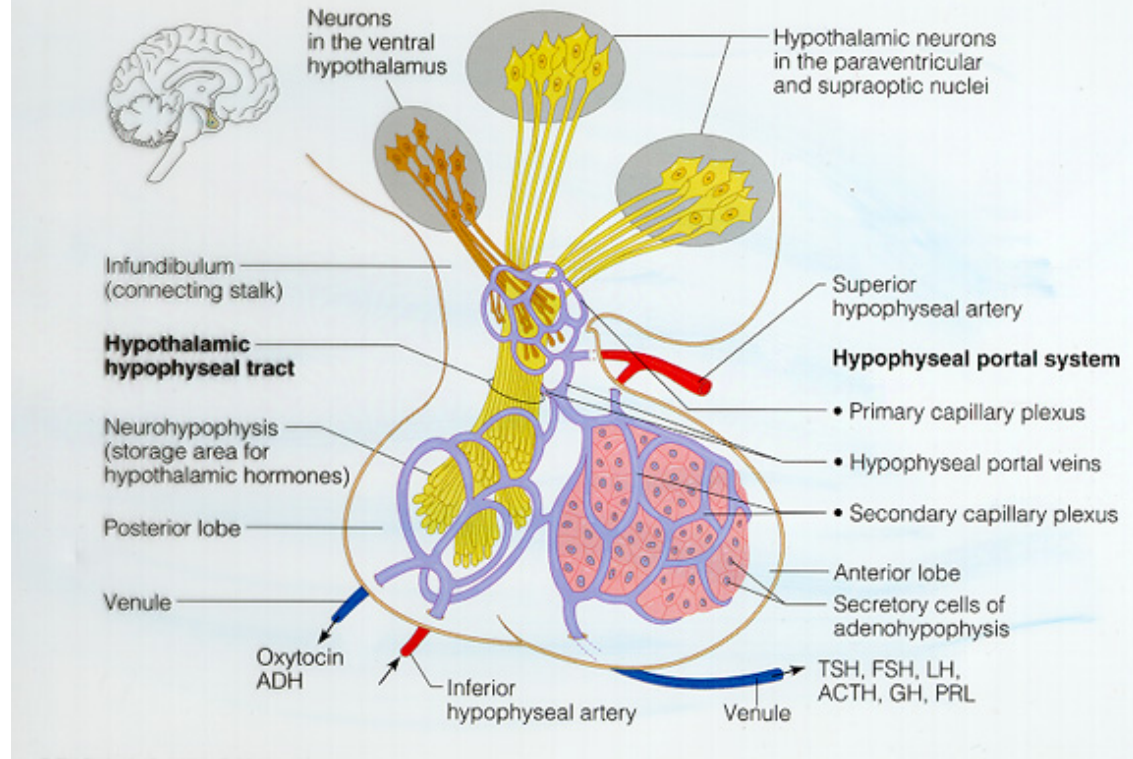


- The adenohypophysis constitutes the anterior $\frac{3}{4}$ of the pituitary. It has two parts
 - a large anterior lobe called the **pars distalis** because it is the most distal to the pituitary stalk
 - **pars tuberalis**- a small mass of cells adhering to the anterior side of the stalk
 - **Pars intermedia**- only seen in the embryo and other animals
 - secretes **melanocyte-stimulating hormone** (MSH) which influences pigmentation of skin, hair, or feathers (not produced in humans)
 - humans produce **proopiomelanocortin** (POMC), which is processed within the pit. to yield smaller fragments such as ACTH and endorphins

- The hypothalamus is connected to the pituitary by a complex of blood vessels called the **hypophyseal portal system**
- the network begins as primary capillaries in the hypothalamus, leading to portal venules that travel down the pituitary stalk to a complex of secondary capillaries in the anterior pituitary.
- The primary capillaries pick up hormones from the hypothalamus, the venules deliver them to the anterior pituitary, and the hormones leave the circulation at the secondary capillaries



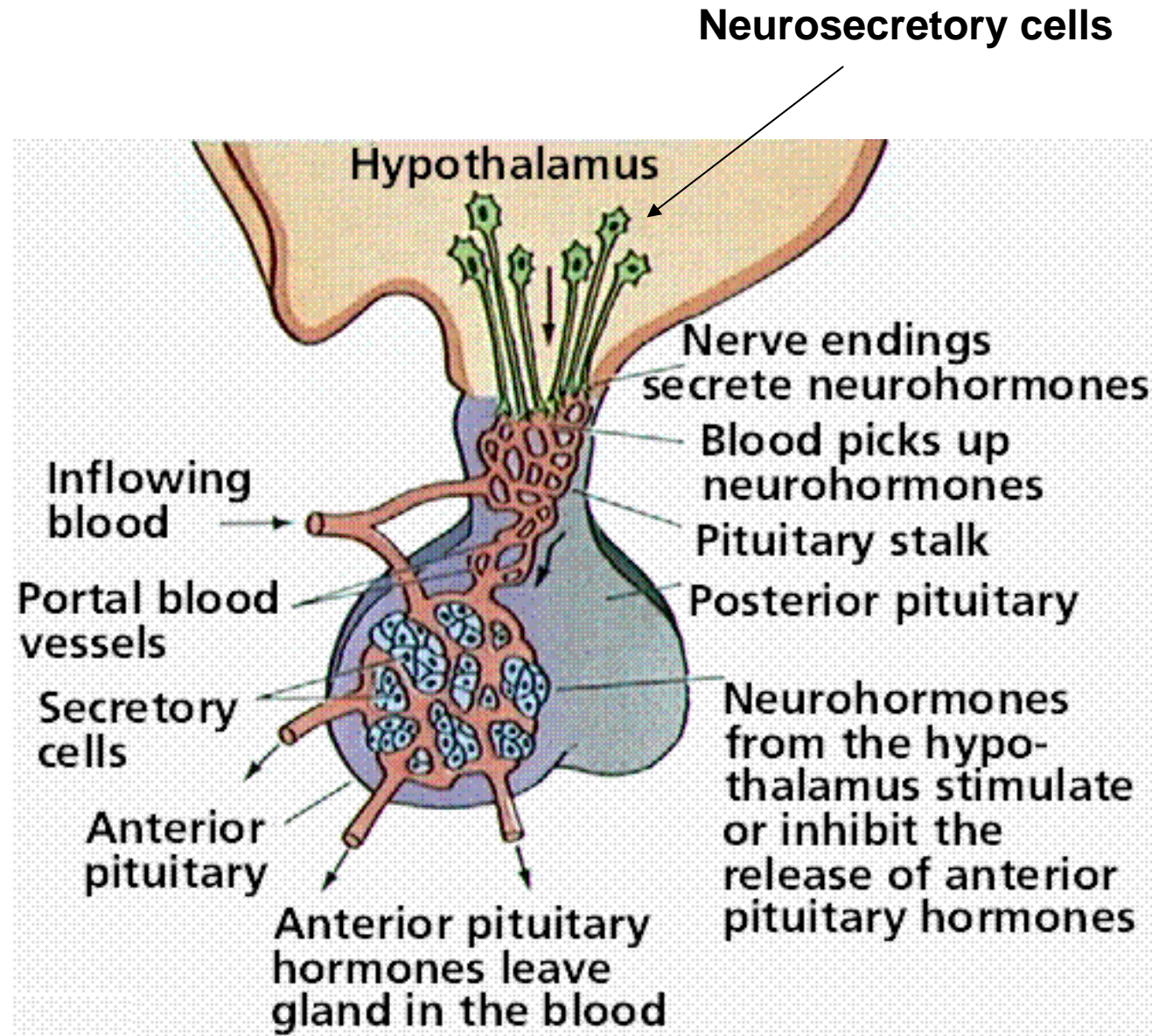
Structural and functional relationships of the pituitary and the hypothalamus (Figure 17.5)



- The neurohypophysis constitutes the posterior quarter of the pituitary.
- Has three parts
 - an extension of the hypothalamus called the median eminence
 - stalk
 - posterior lobe (pars nervosa)- the largest part

- The neurohypophysis is **not a true gland** but a **mass of neuroglia and nerve fibers**.
- The **nerve fibers arise from cell bodies in the hypothalamus**, travel down the stalk as a bundle called the **hypothalamo-hypophyseal tract** and end in the posterior lobe
- The **hypothalamic neurons synthesize hormones**, transport them down the stalk, and store them in the post pit. until a nerve signal triggers their release

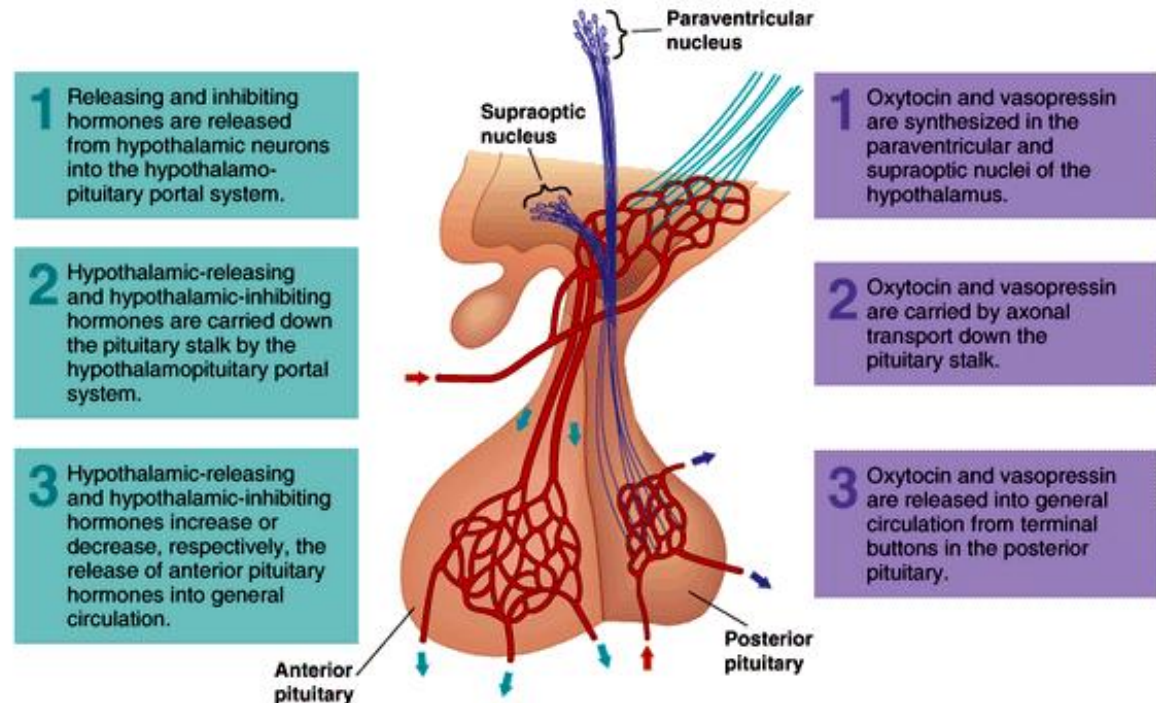
Hypothalamic hormones reach the anterior pituitary via the **hypophyseal portal system** (carries blood between two capillary networks without passing through the heart)



Anterior Pituitary Gland (Adenohypophysis)

- Hormone secretion regulated by
 - **releasing hormones** and **inhibiting hormones** from the hypothalamus
 - Negative feedback from hormones of target glands that act on Ant. Pit and thypothalamus

► Control of the Anterior and Posterior Pituitary by the Hypothalamus



Hypothalamus produces nine hormones

- Seven of them travel through the portal system and regulate the activities of the ant. pit.
 - Five are releasing hormones that stimulate the ant. pit to secrete its hormones
 - gonadotropin releasing hormone
 - thyrotropin releasing hormone
 - corticotropin releasing hormone
 - prolactin releasing hormone
 - growth hormone releasing hormone
 - two are inhibiting hormones that suppress pituitary secretion
 - prolactin inhibiting hormone
 - somatostatin
- Most of these hypothalamic hormones control the release of just one ant. pit. hormone
 - Except gonadotropin-releasing hormone which controls the release of both FSH and LH

- The other two hypothalamic hormones are secreted by way of the posterior pituitary
 - **Oxytocin**- made by the neurons in the paraventricular nuclei of the thalamus
 - **antidiuretic hormone (vasopressin)**- produced mainly by the supraoptic nuclei

5 Types of Anterior Pituitary Cells

- Hormones secreted by cells that influence another endocrine gland are called **tropic hormones** or **tropins**
- **Thyrotrophs**- secrete **TSH** that controls the thyroid gland
- **Gonadotrophs**-secrete **LH** and **FSH** that controls the ovary and testes
- **Corticotrophs**-secrete **ACTH** that controls the adrenal gland function

Non-tropic

- **Lactotrophs**- secretes prolactin (**PRL**) that controls milk production in the breast
- **Somatotrophs**- secreted growth hormone (**GH**) that stimulates several tissues to secrete insulin-like growth factors, hormones that stimulate general body growth

- The hormonal relationship between the hypothalamus, pituitary, and a more remote endocrine gland is called an **axis**.
- There are 3 axis
 - hypothalamic-pituitary-gonadal axis
 - hypothalamic-pituitary-thyroidal axis
 - hypothalamic-pituitary-adrenal axis

Actions of Pituitary Hormones

Anterior Pituitary

- **FSH-** (produced by **gonadotropes**) stimulates the ovary to develop eggs and sperm production in males
- **LH-** (produced by **gonadotropes**) stimulates ovulation and the corpus luteum to secrete estrogen and progesterone
 - stimulates interstitial cells of the testes to secrete testosterone
- **TSH-** (produced by **thyrotropes**) stimulates growth of the thyroid gland and the secretion of thyroid hormone
- **ACTH-** (produced by **corticotropes**) stimulates the adrenal cortex to secrete its hormones (corticosteroids), especially cortisol, which regulates glucose, fat, and protein metabolism. It also plays a central role in stress.

Actions of Pituitary Hormones (cont)

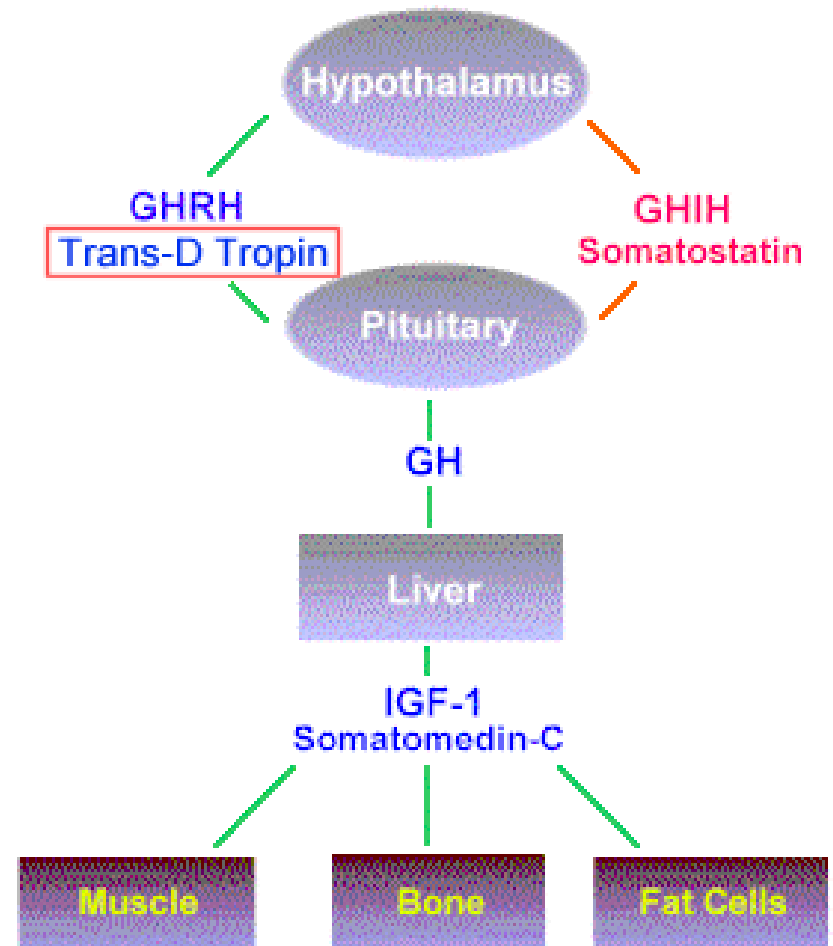
Anterior pituitary (cont)

- **Prolactin**- secreted by **lactotropes**, which increase greatly in size and number during pregnancy
 - has no effects until after birth
 - stimulates the mammary glands to synthesize milk
 - In males, it makes the testes more sensitive to LH, thus, it indirectly enhances the secretion of testosterone
- **Growth Hormone (somatotropin)**- (produced by **somatotropes**) has the general effect of promoting mitosis and cellular differentiation thus to promote widespread tissue growth

Human Growth Hormone from Somatotrophic Cells

- **Somatotrophs-**

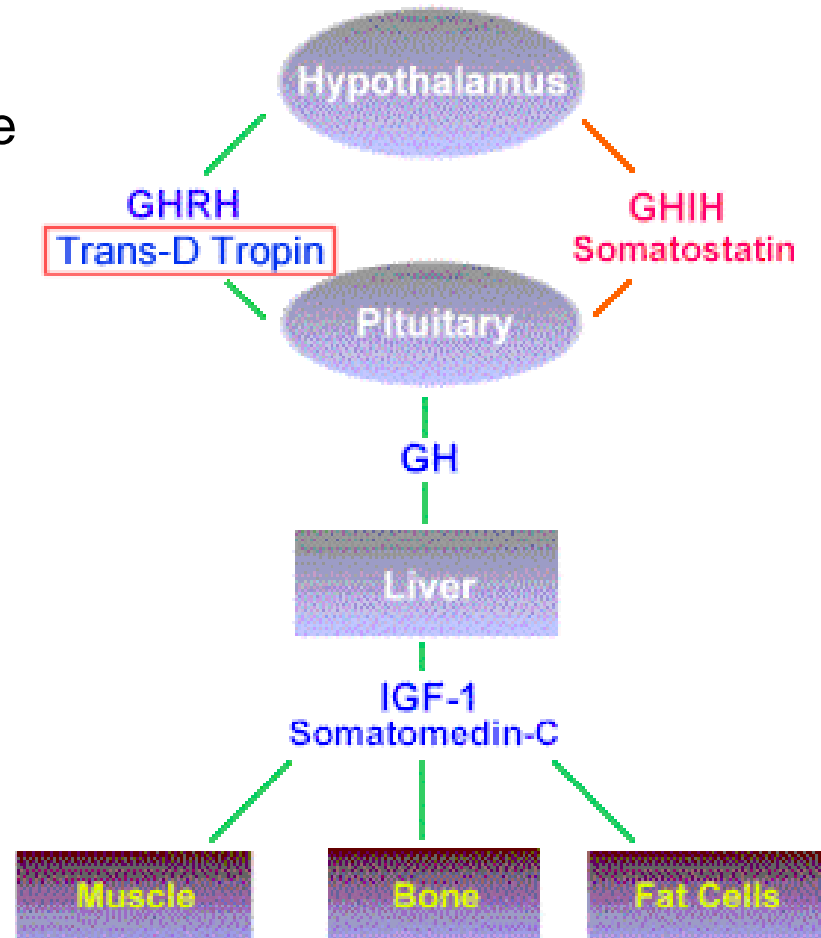
- most numerous cells in the ant. pit
- secrete human growth hormone (hGH) or **somatotropin**
- general effect is to promote widespread tissue growth
- Has widespread effects on the body, especially cartilage, bone, muscle, and fat
- hGH stimulates these tissues to secrete **insulin-like growth factors (IGF-I or II) or somatomedins** that causes cells to grow and multiply by
 - Increasing uptake of amino acids
 - Accelerating protein synthesis
- GH is short lived (half life of 6-20 min), IGFs, by contrast, have life of about 20 hr., so they greatly prolong the effects of GH



Human Growth Hormone from Somatotrophic Cells

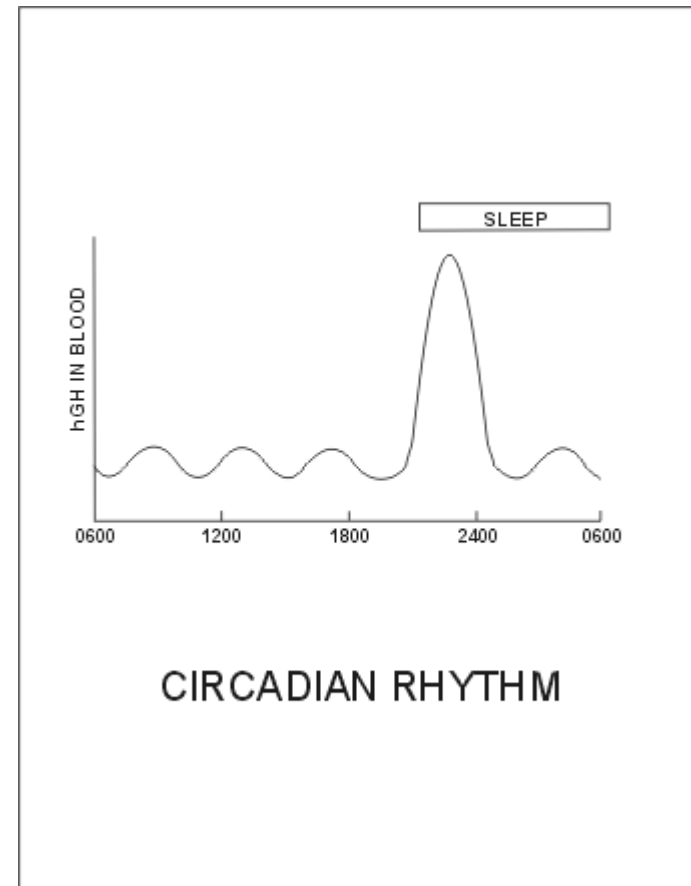
Other Actions of IGFs

- Decreases the breakdown of proteins and the use of amino acids for ATP production. **(protein sparing effect)**
- Enhances lipolysis in adipose tissue resulting in increase use of fatty acids for ATP production by body cells
- Decrease glucose uptake, there by decreasing the use of glucose for ATP production by most body cells **(glucose sparing effect)**
 - Spares glucose for use by neurons
 - Stimulate liver cells to release glucose into the blood
- promotes Na^+ , K^+ , and Cl^- retention by the kidney, enhances Ca^{2+} absorption by the small intestine, and makes these electrolytes available to the growing tissues



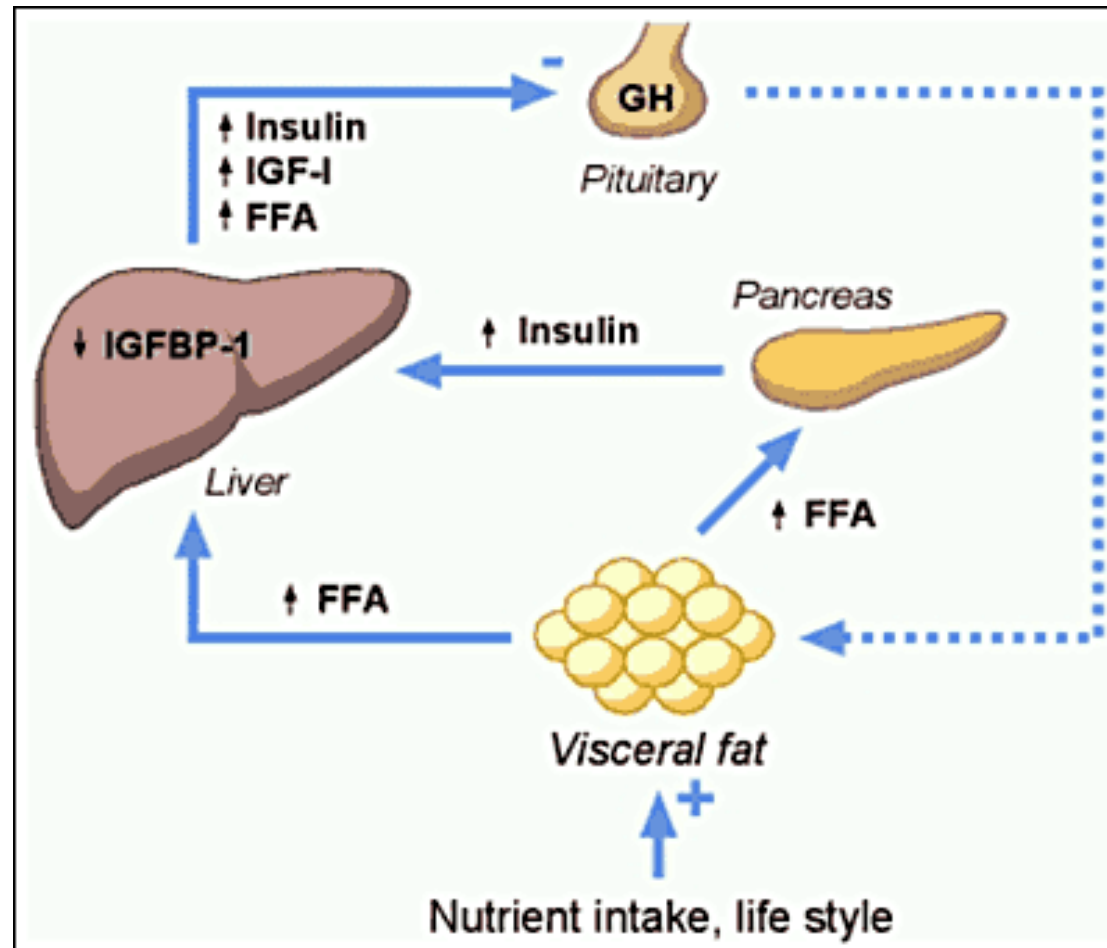
Human Growth Hormone from Somatotrophic Cells

- GH secretion occurs in a pulsatile fashion, and in a circadian rhythm with a maximal release in the second half of the night.
- Release is controlled by two hypothalamic hormones
 - Growth hormone releasing hormone (GHRH)- promotes secretion of hGH
 - Growth hormone inhibiting hormone (GHIH)-
(somatostatin) (SST)- suppresses release



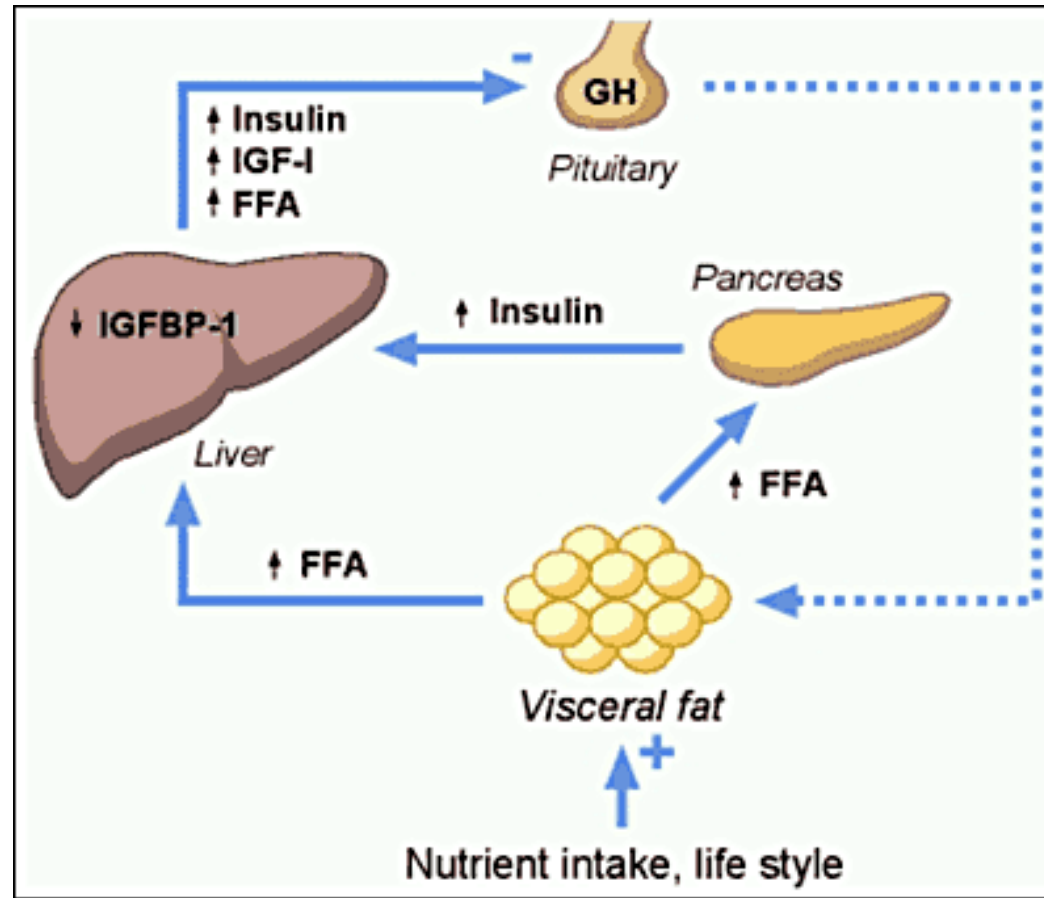
Human Growth Hormone from Somatotrophic Cells

- A major regulator of GHRH and GHIH secretion is blood glucose levels
 - Hypoglycemia- stimulates hypothalamus to secrete GHRH, causing ant. pit. to release GH
 - Hyperglycemia- stimulates hypothalamus to release GHIH, which inhibits the release of GHRH and causes the inhibition of the ant. pit. to release of GH
 - Results in decrease IGFs breakdown of glycogen in the liver



Human Growth Hormone from Somatotrophic Cells

- Factors that promote secretion of GH
 - Stress & exercise-causing increased activity of the sympathetic nervous system
 - hypoglycemia
 - and ingestion of protein (high levels of circulating amino acids)
 - Low levels of FFA
 - Deep sleep (stages 3 and 4 of non-rapid eye movements sleep)
 - High levels of glucose and FFA inhibits secretion
 - Other hormones- glucagon, estrogens, cortisol, and insulin



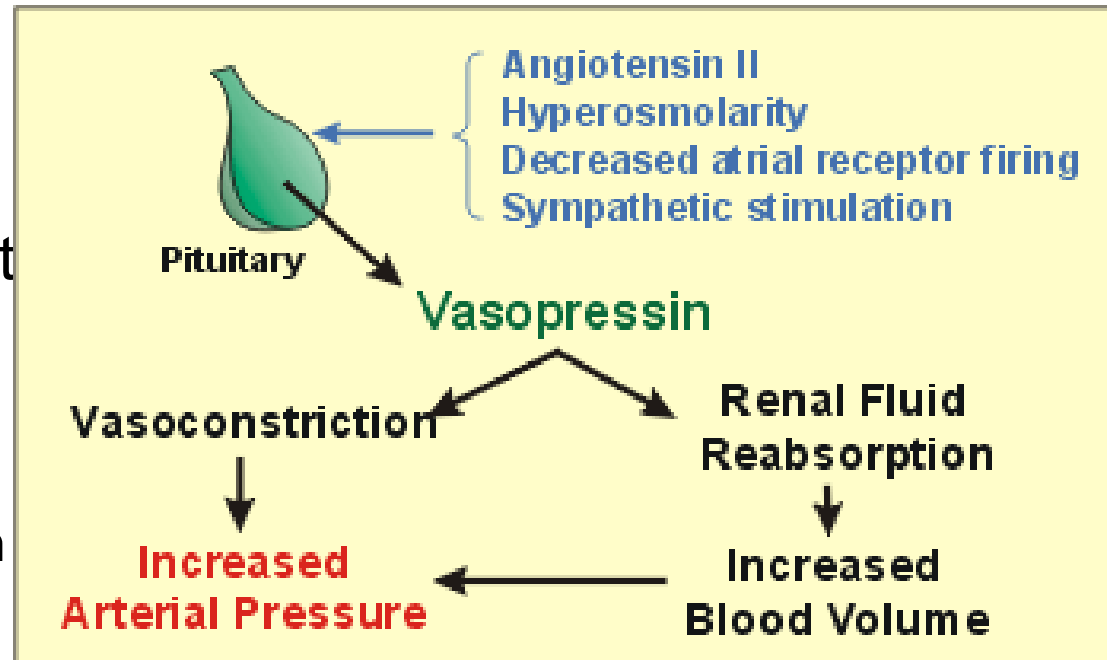
Human Growth Hormone from Somatotrophic Cells

- Factors that inhibit hGH secretion
 - Increased blood fatty acids
 - Decreased blood amino acids
 - Rapid eye movement sleep
 - Emotional deprivation
 - Obesity
 - Low levels of thyroid hormones
 - hGH itself through negative feedback

Actions of Pituitary Hormones

Posterior Pituitary

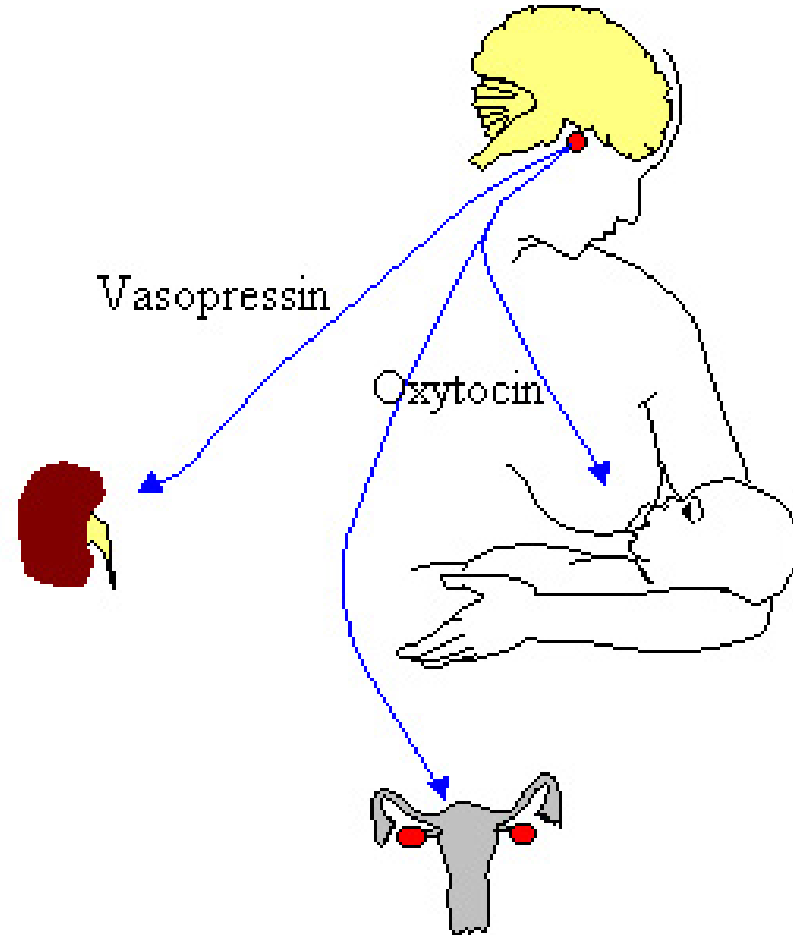
- **ADH**- acts on the kidney to increase water retention, reduce urine volume, and help prevent dehydration
 - also called **vasopressin** because it causes vasoconstriction at high concentrations (these high concentrations are unnatural in humans, except in pathological states)
 - functions as a brain neurotransmitter
 - maybe called **arginine vasopressin (AVP)**



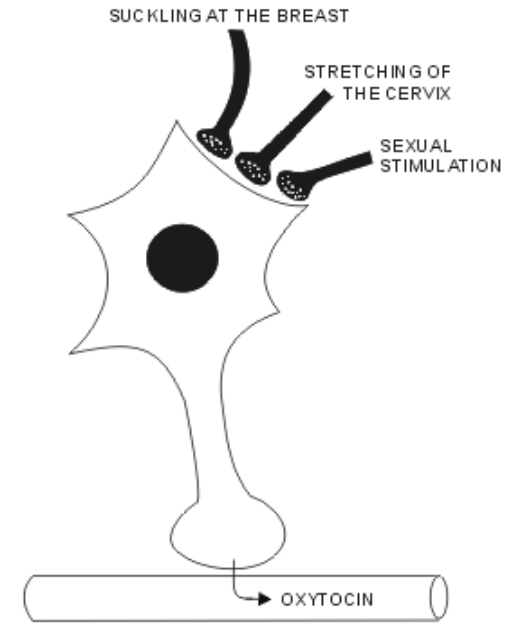
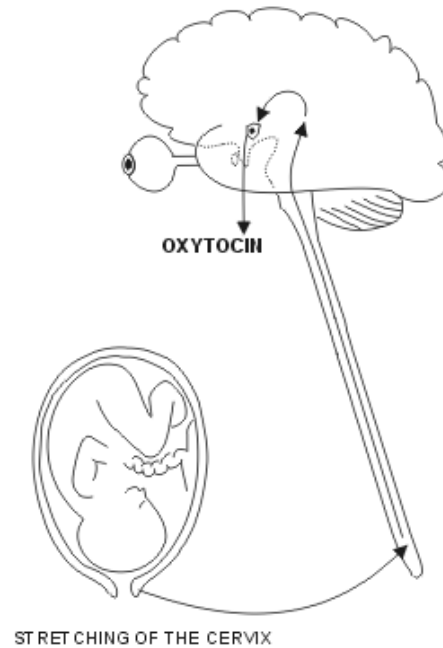
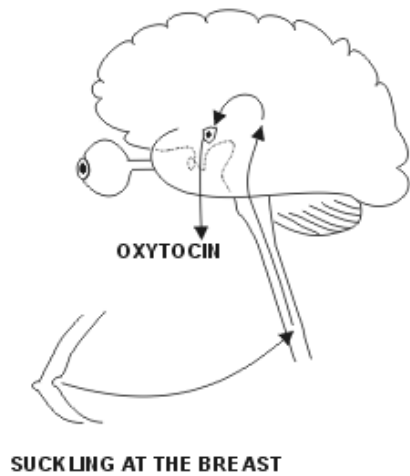
Actions of Pituitary Hormones

Posterior Pituitary (cont)

- **Oxytocin**- has various reproductive roles
 - in childbirth, it stimulates smooth muscle of the uterus to contract, thus contributing to labor contraction.
 - In lactating mothers- it stimulates milk let down by causing smooth muscle contraction of mammary glands
 - In both sexes OT secretion surges during sexual arousal and orgasm
 - may play a role in semen expulsion and uterine contraction that helps transport sperm up in to the female reproductive tract, and in the feeling of sexual satisfaction and emotional bonding

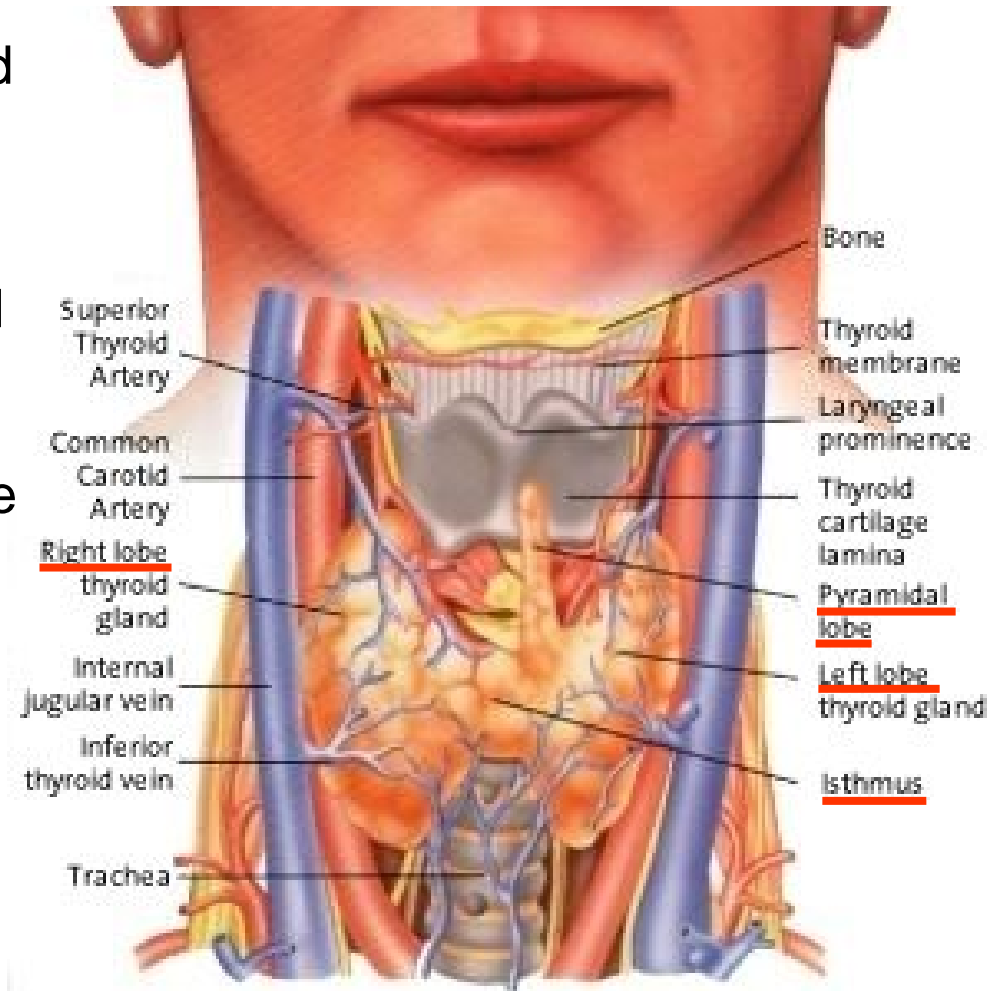


Oxytocin Stimulation



Thyroid Gland

- Butterfly shaped organ located just inferior to the larynx
- Composed of right and left lateral lobes that lie on each side of the trachea, connected by an isthmus anterior to the trachea
- A small pyramidal shaped lobe sometimes extends upward from the isthmus
- Normal mass is about 30g (1oz)
- Is highly vascularized



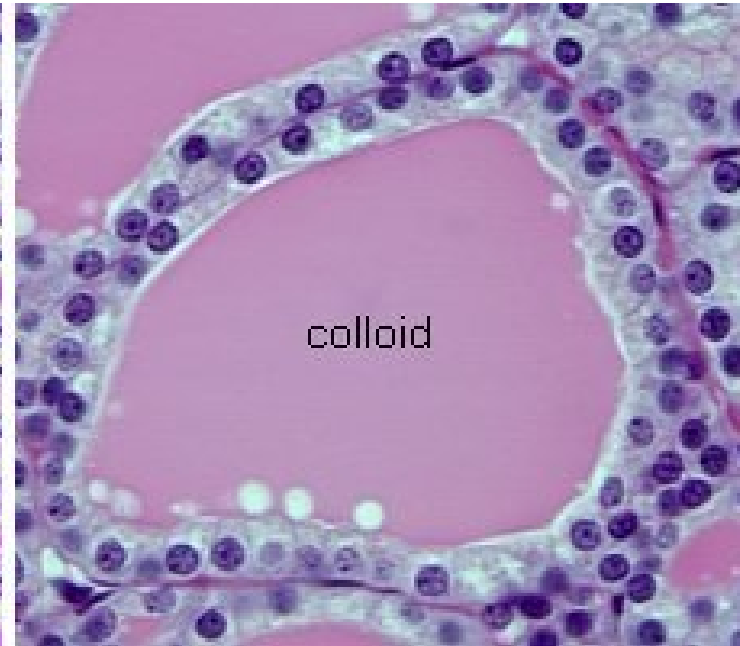
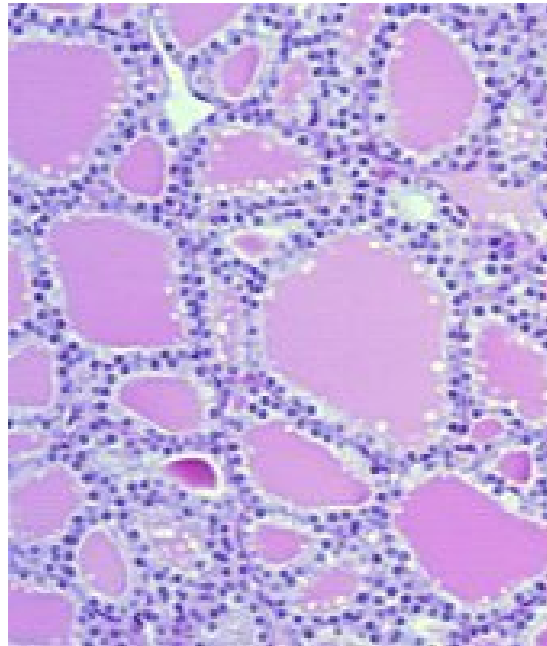


Thyroid Gland

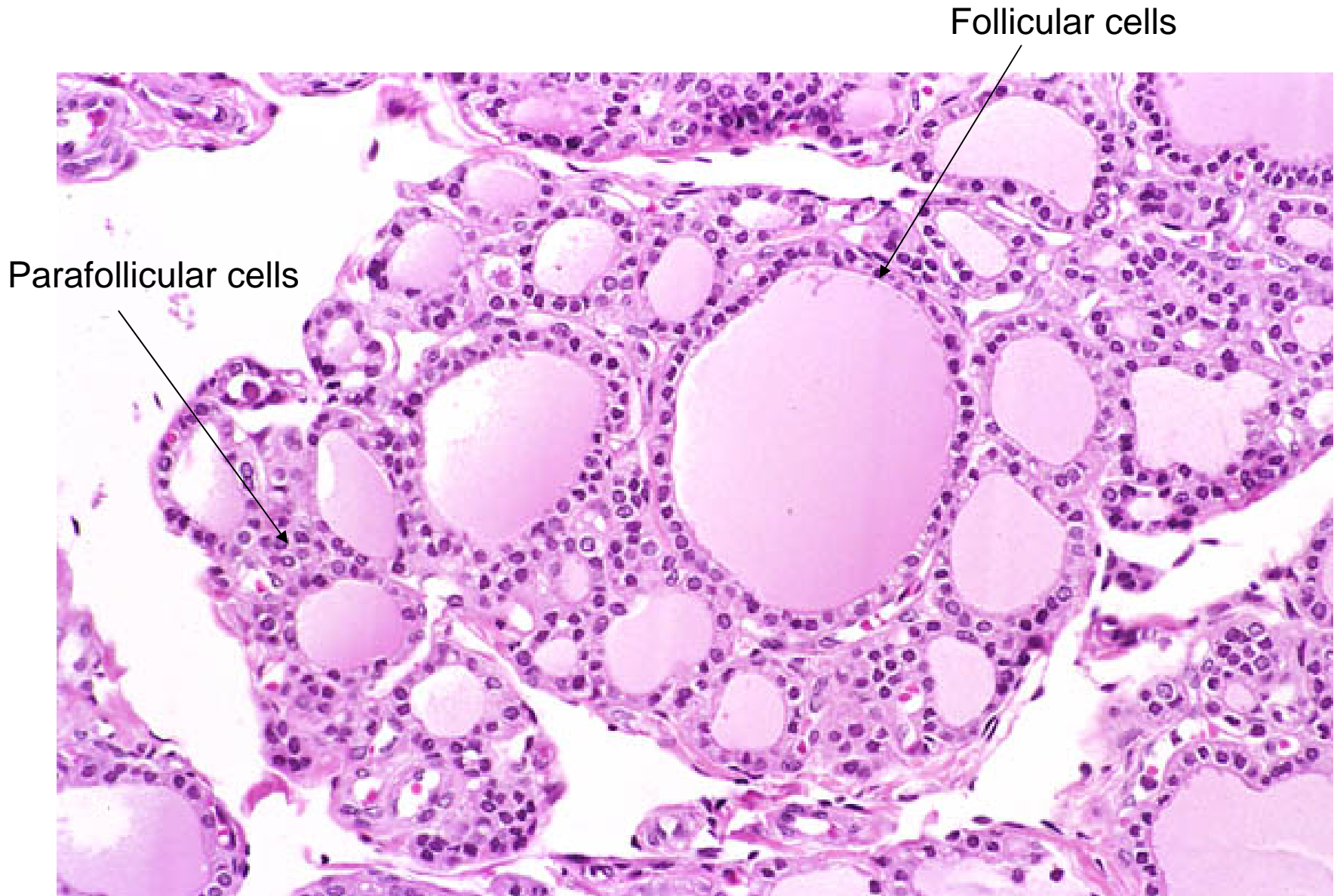
This is the normal appearance of the thyroid gland on the anterior trachea of the neck. The thyroid gland has a right lobe and a left lobe connected by a narrow isthmus. The normal weight of the thyroid is 10 to 30 grams. It cannot easily be palpated on physical examination.

Thyroid Gland

- **Thyroid follicles** make up most of the thyroid gland
 - The wall of each follicle consists primarily of cuboidal to low columnar cells called **follicular cells** surrounded by a basement membrane
- **Parafollicular cells** (C cells) lie between follicles that produce **calcitonin** which helps regulate calcium

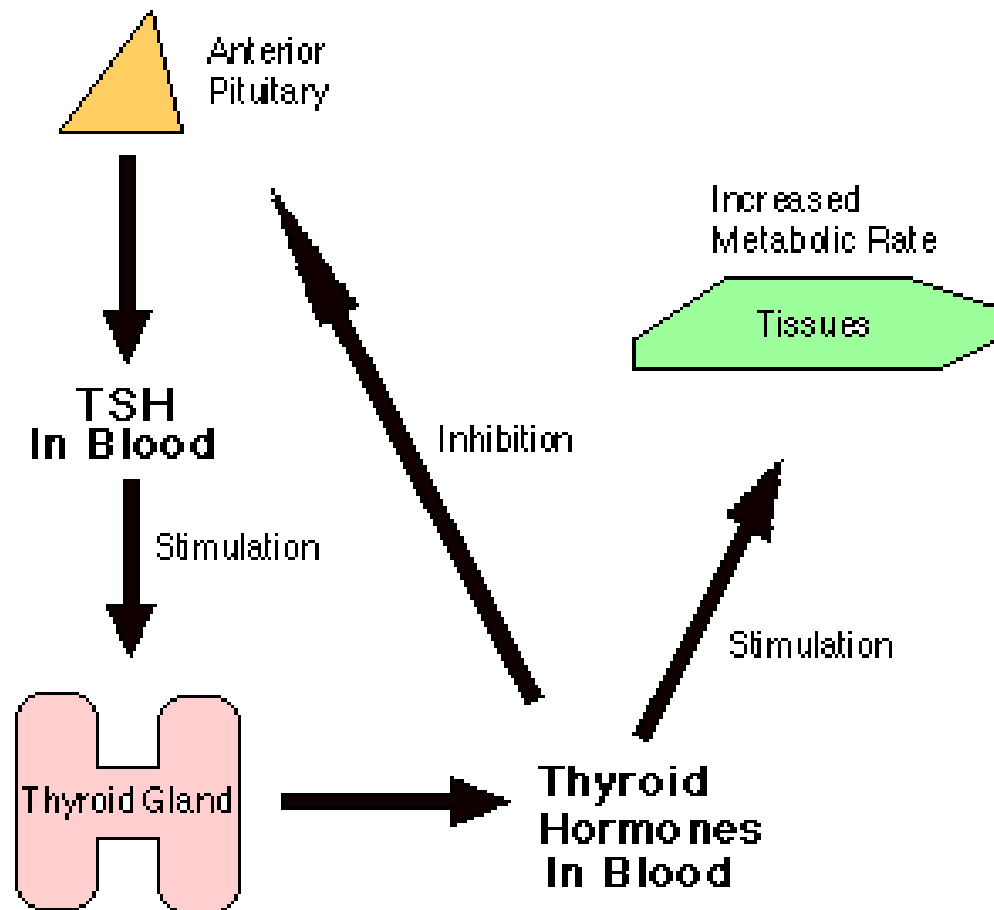


Thyroid Gland



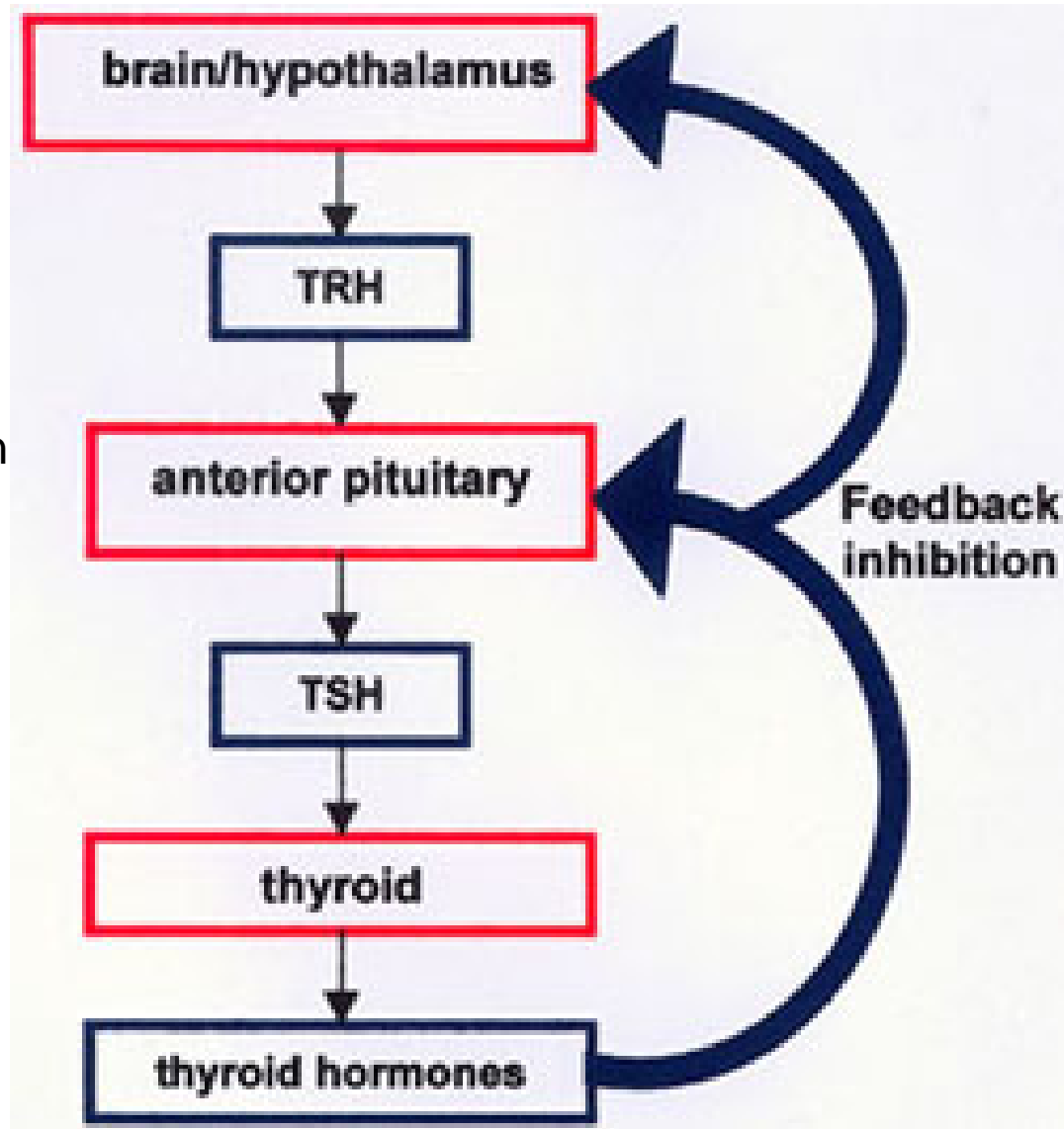
Thyroid Gland

- **Thyrotropin-releasing hormone (TRH)** from the hypothalamus controls the secretion of thyroid-stimulating hormone (TSH) from the ant pit.
- TSH stimulates the synthesis of **thyroxine (T4)** and **triiodothyronine (T3)**
- T4 and T3 inhibit TRH by negative feedback
- There is no thyrotropin inhibiting hormone



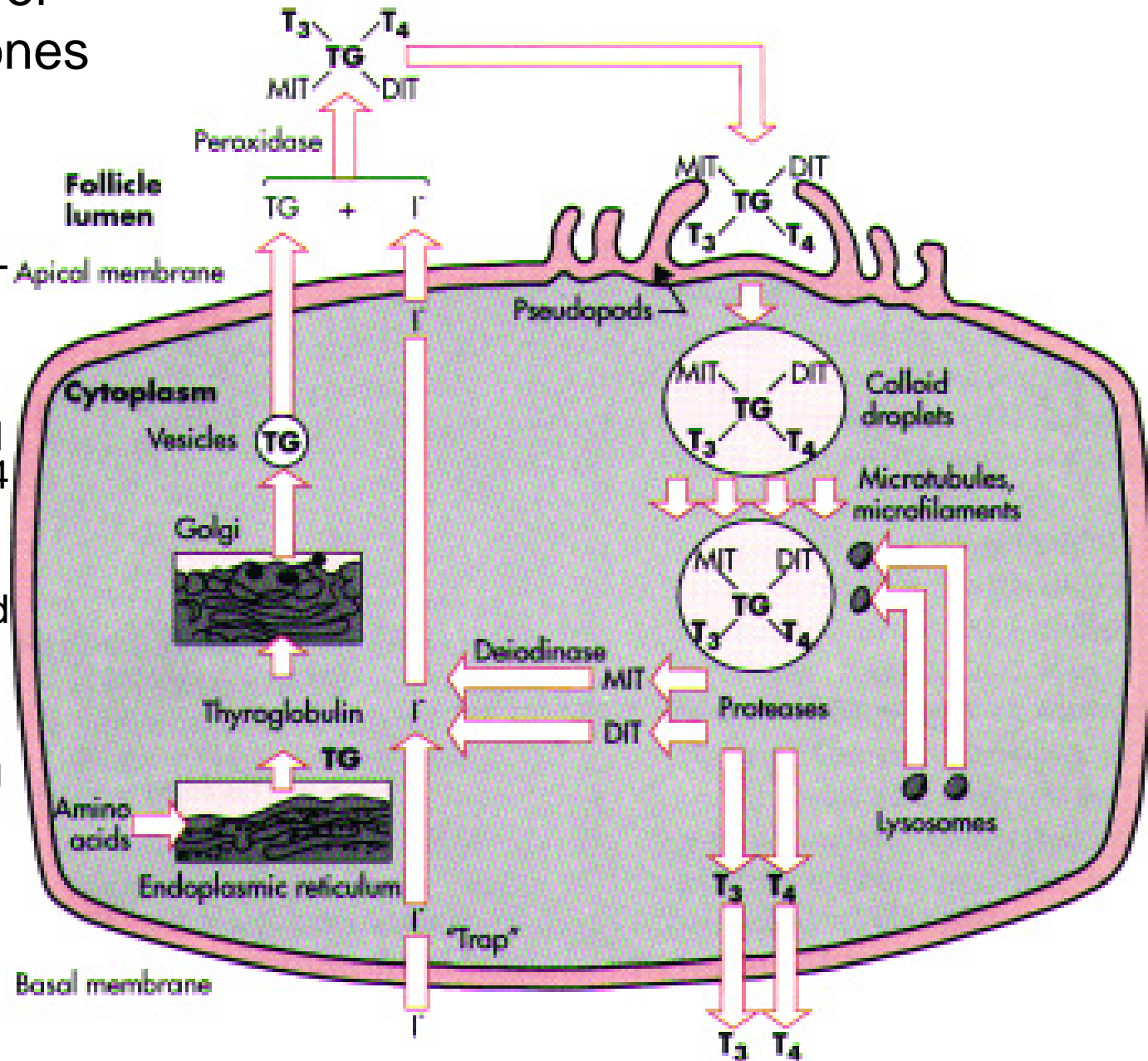
Thyroid Gland

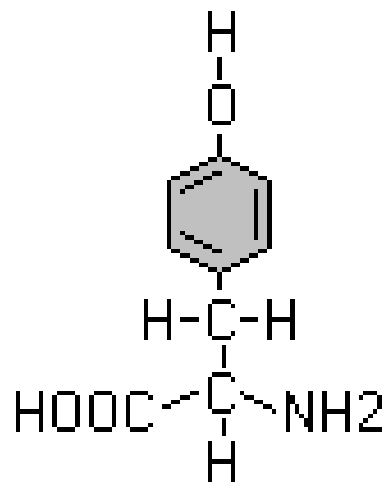
- T4 and T3 inhibit TRH by negative feedback
- There is no thyrotropin inhibiting hormone
- Primary effect is to increase the body's metabolic rate and as a result it:
 - raises body O₂ consumption
 - increases heat production (calorigenic effect)
 - raises heart and breathing rate
 - increase breakdown of carbohydrates, fats, and protein for fuel and stimulates appetite
 - stimulates pit. to secrete GH
- Factors that increase TSH secretion
 - Conditions that increase ATP demand
 - Cold environment
 - Hypoglycemia
 - High altitude
 - pregnancy



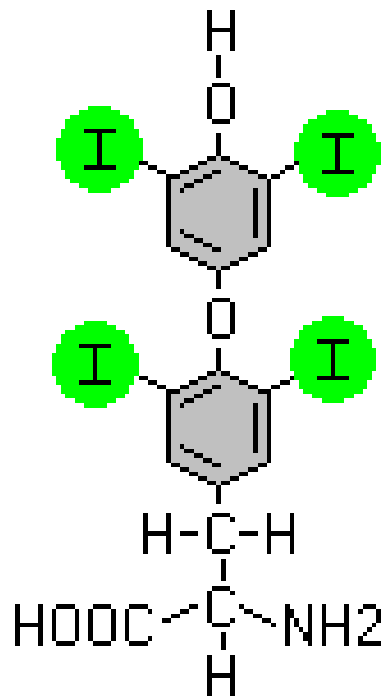
Formation, Storage, and Release of Thyroid Hormones

- Iodide trapping
- Synthesis of thyroglobulin
- Oxidation of iodide- 2I^- to I_2
- Iodination of tyrosine
- Coupling of T1 and T2 to form T3 or T4
- Pinocytosis and digestion of colloid
- Secretion of thyroid hormones
- Transport in the blood attached to **thyroxine-binding globulin (TGB)**
- More than 99% of thyroid hormone is bound to carrier proteins



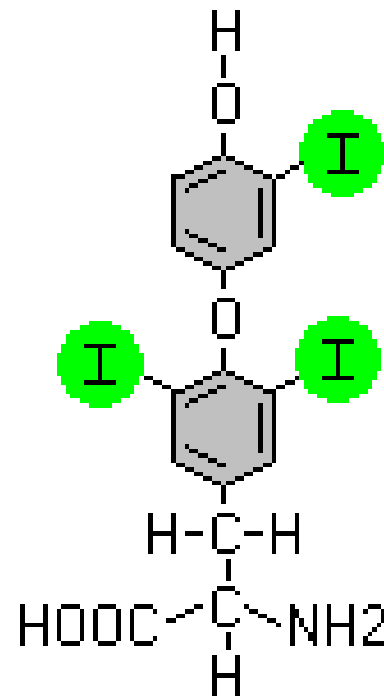


Tyrosine



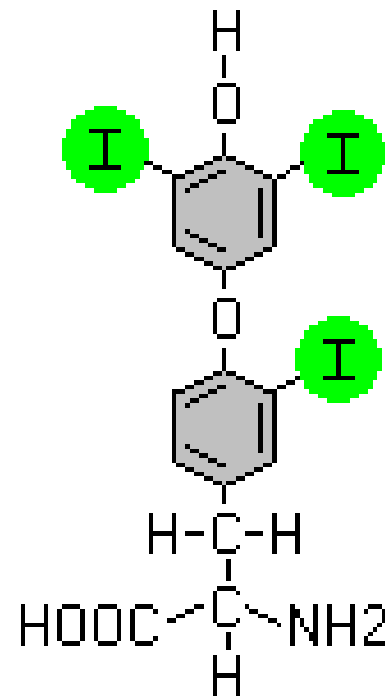
Thyroxine (T4)

Secreted in greater quantity and converted to T3 in the cell

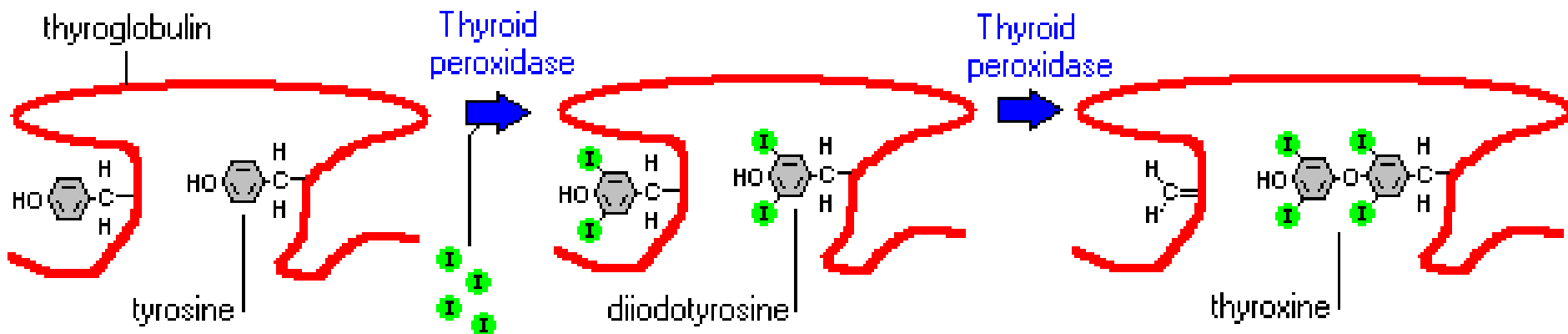


Triiodothyronine (T3)

More potent



"Reverse T3" (inactive)



Thyroid Gland

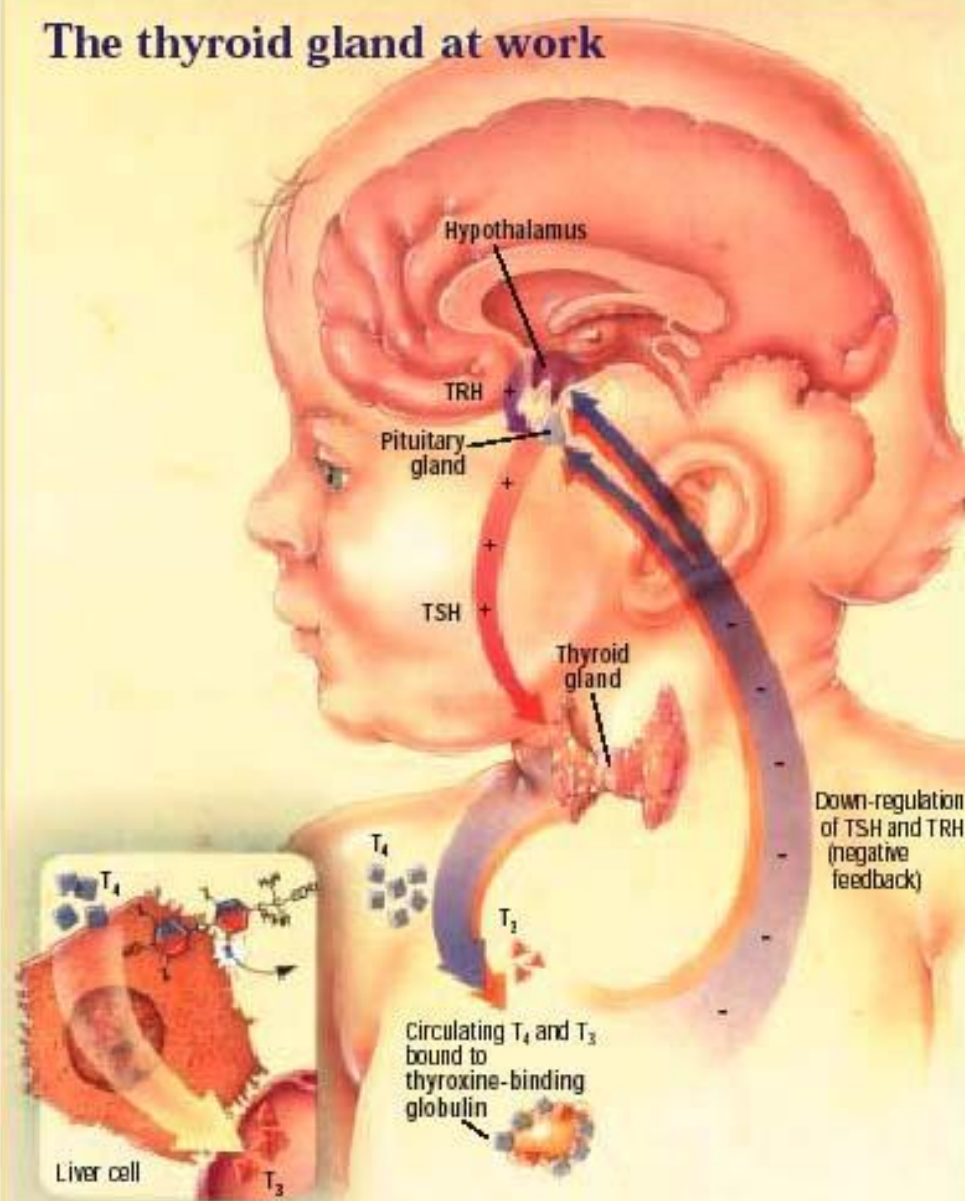
Actions of Thyroid Hormones (cont)

- Effects most body cells- most body cells have receptors
- Regulate
 - **Basal metabolic rate (BMR)- the rate of oxygen use at rest after an overnight fast-** increase by stimulating the use of cellular oxygen to produce ATP
 - **Calorigenic effect-** increase body temperature by causing an increase use of ATP (by increasing Na/K pumps which are heavy users of ATP)
 - Regulate metabolism by stimulating
 - stimulate of protein synthesis and
 - increase use of glucose and fatty acids for ATP production
 - Increase lipolysis and enhanced cholesterol excretion (reducing cholesterol levels)

Thyroid Gland

- Enhances actions of catecholamines (norepinephrine, and epinephrine) by up-regulating beta receptors (contributes to symptoms of hyperthyroidism)
 - Symptoms of hyperthyroidism
 - Increased heart rate
 - More forceful heartbeat or contractions
 - Increased blood pressure
- Together with human growth hormone and insulin, thyroid hormones accelerates body growth, particularly the nervous tissue.

The thyroid gland at work



The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates release of thyroid-stimulating hormone (TSH) by the pituitary gland. TSH causes the thyroid to release thyroxine (T_4) and, to a lesser degree, triiodothyronine (T_3). The inset shows conversion of T_4 to T_3 by deiodination by the liver. Other tissue, including the kidney, brown adipose tissue, muscle, and the central nervous system, can also convert T_4 to T_3 .

Congenital Hypothyroidism (Cretinism)

- Severe mental retardation if not treated promptly (before aprox. 3 months of life)
- Normal at birth because protected by maternal hormone that crosses the placenta to allow normal development
- Most states require testing of all newborns
- Oral hormone must be started soon after birth and continued for life



Sufferers have mental impairment and often suffer from dwarfism as their linear growth is affected.

TABLE 2

Signs and symptoms of hypothyroidism in a newborn

Facial puffiness
 Large tongue
 Large anterior or posterior fontanelle
 Cold hands or feet
 Hypotonia
 Lethargy
 Hypothermia
 Poor weight gain
 Poor feeding
 Respiratory distress in an infant weighing >2.5 kg
 Delayed passage of stools
 Prolonged unconjugated hyperbilirubinemia

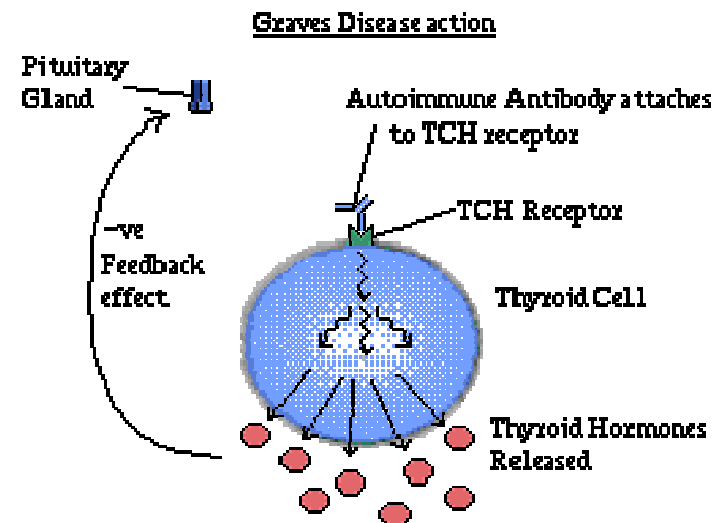
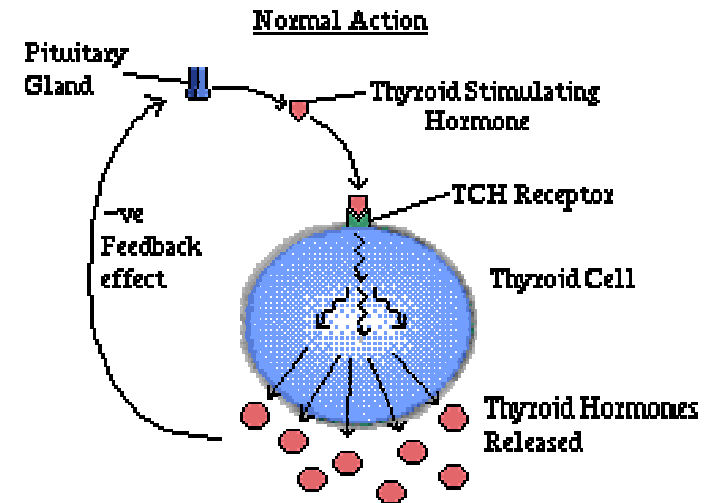
Myxedema

- Hypothyroidism during the adult years
- Hallmark is edema that causes the facial tissues to swell and look puffy
- Slow heart rate
- Low body temperature
- Sensitivity to cold
- Dry hair and skin
- Muscular weakness
- General lethargy
- Tendency to gain weight easily

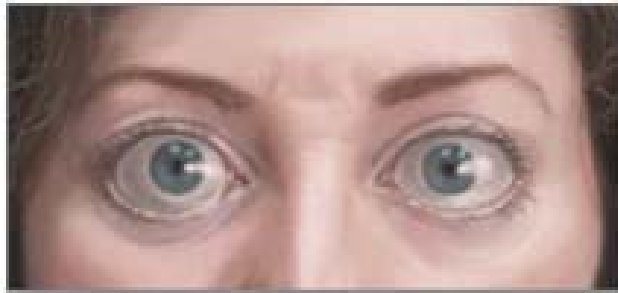


Hyperthyroidism (Graves Disease)

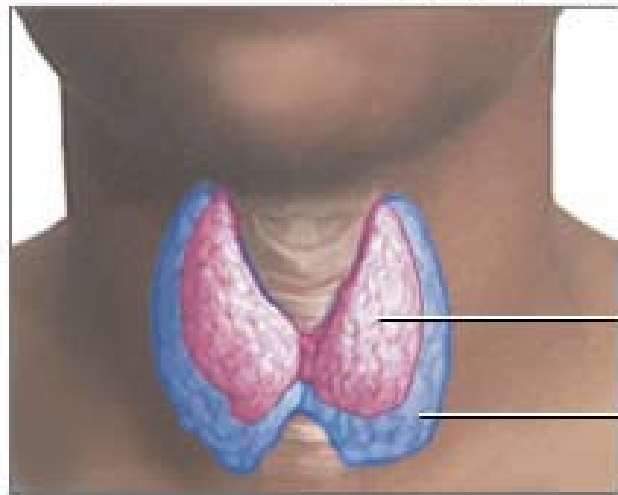
- Occurs seven to ten times more in females than males
- Production of antibodies that mimic the actions of thyroid stimulating hormone
 - Continually stimulate the thyroid to produce thyroid hormone
- Primary sign is enlarged thyroid
- **Exophthalmos**- edema behind the eyes, which cause the eyes to protrude



Signs of Hyperthyroidism



Exophthalmos (bulging eyes)



Normal thyroid

Enlarged thyroid

Diffuse goiter

- diffuse goiter (enlarged thyroid gland)
- rapid pulse
- weight loss and trembling
- ophthalmopathy (bulging eyes)
- pretibial myxedema (swelling of shins)

- Jitteriness, shaking, increased nervousness, irritability
- Rapid heart beat or palpitations
- Feeling hot

- Fatigue, feeling exhausted
- More frequent bowel movements
- Shorter or lighter menstrual periods

Treatment

- Thyroidectomy
- Radioactive iodine (destroy thyroid tissue)
- Antithyroid drugs to block synthesis of thyroid hormones

Graves' disease





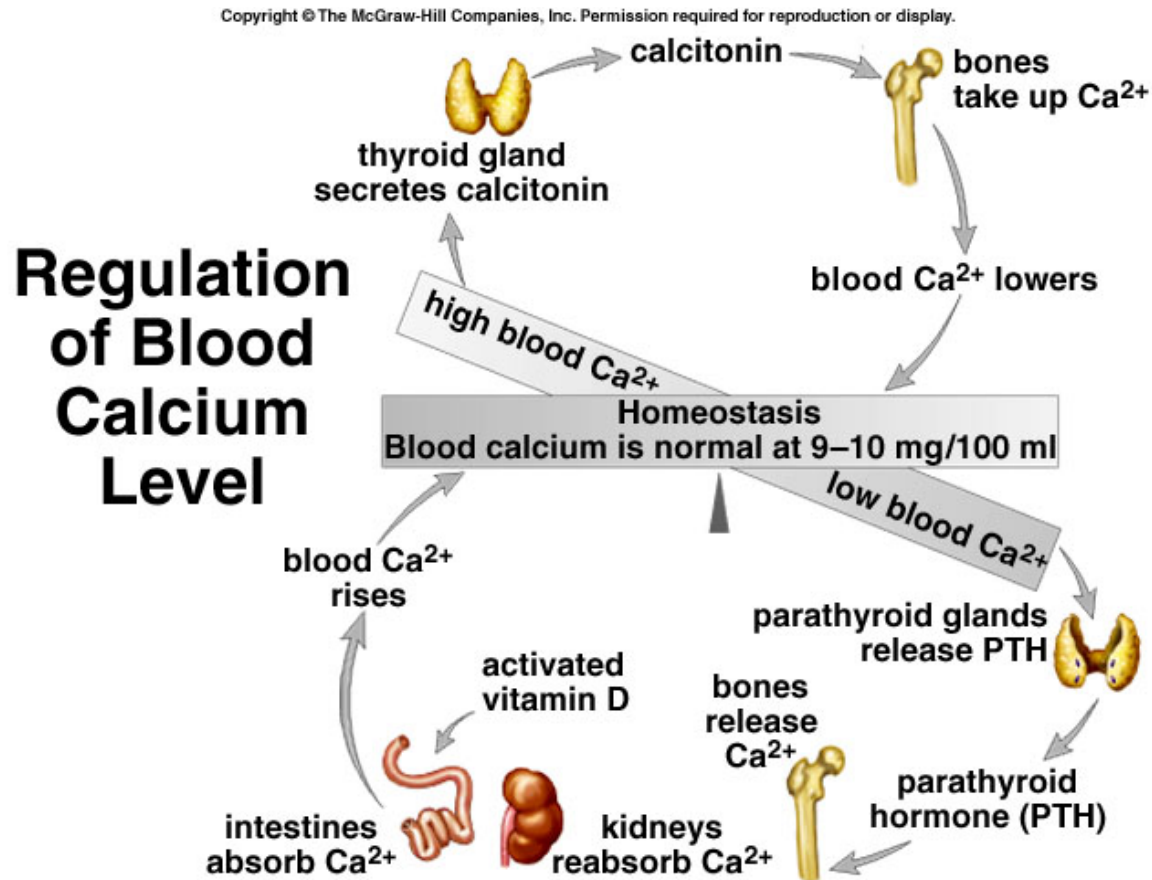
A simple, or endemic , goiter us caused by insufficient iodine in the diet.

Goiter- This diffusely enlarged thyroid gland is somewhat nodular. This patient was euthyroid. This represents the most common cause for an enlarged thyroid gland and the most common disease of the thyroid--a nodular goiter.



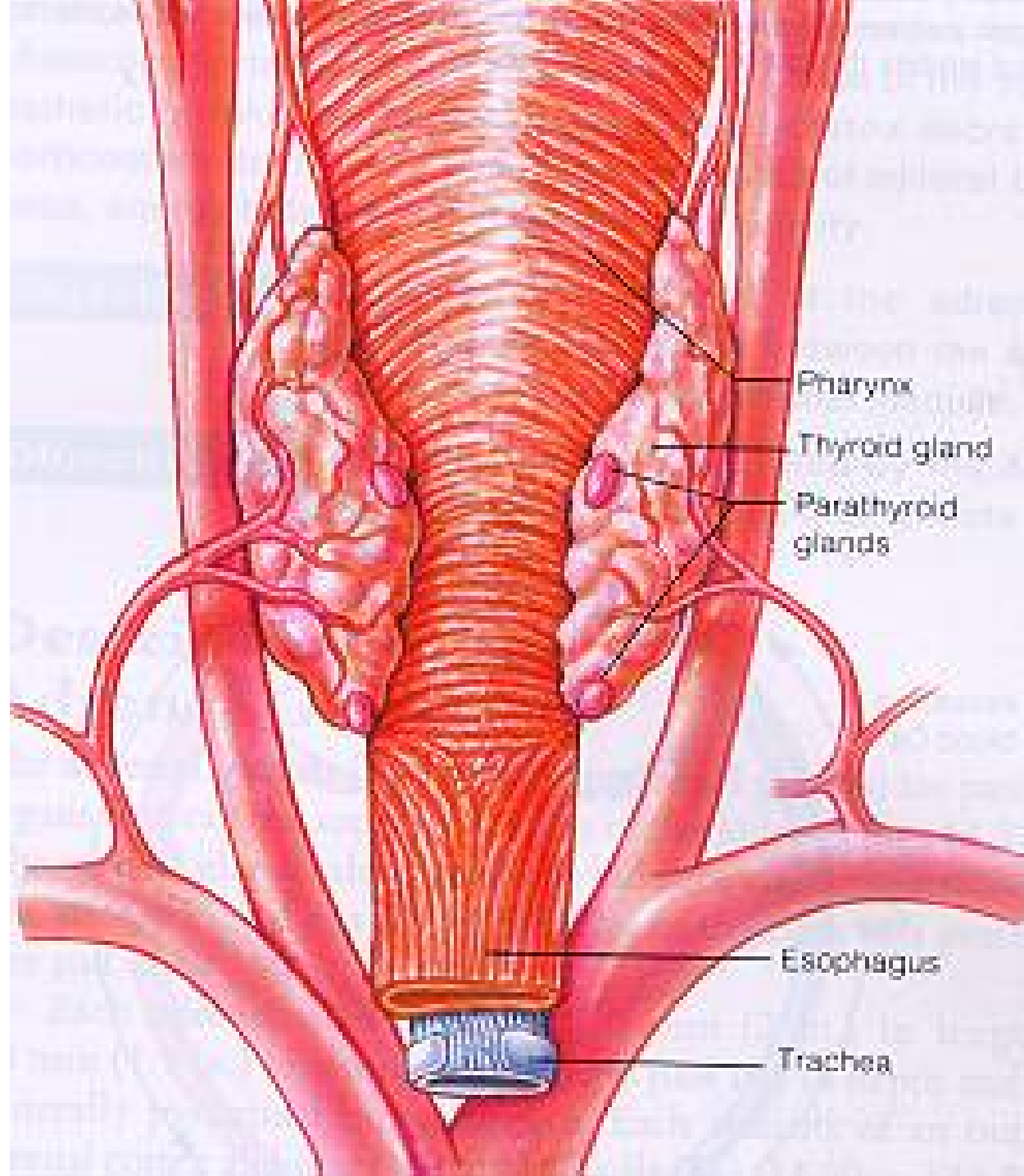
Calcitonin

- Produced by parafollicular cell of the thyroid
- Decrease blood calcium levels by
 - inhibiting bone resorption by osteoclasts
 - Accelerating uptake of calcium and phosphates into bone



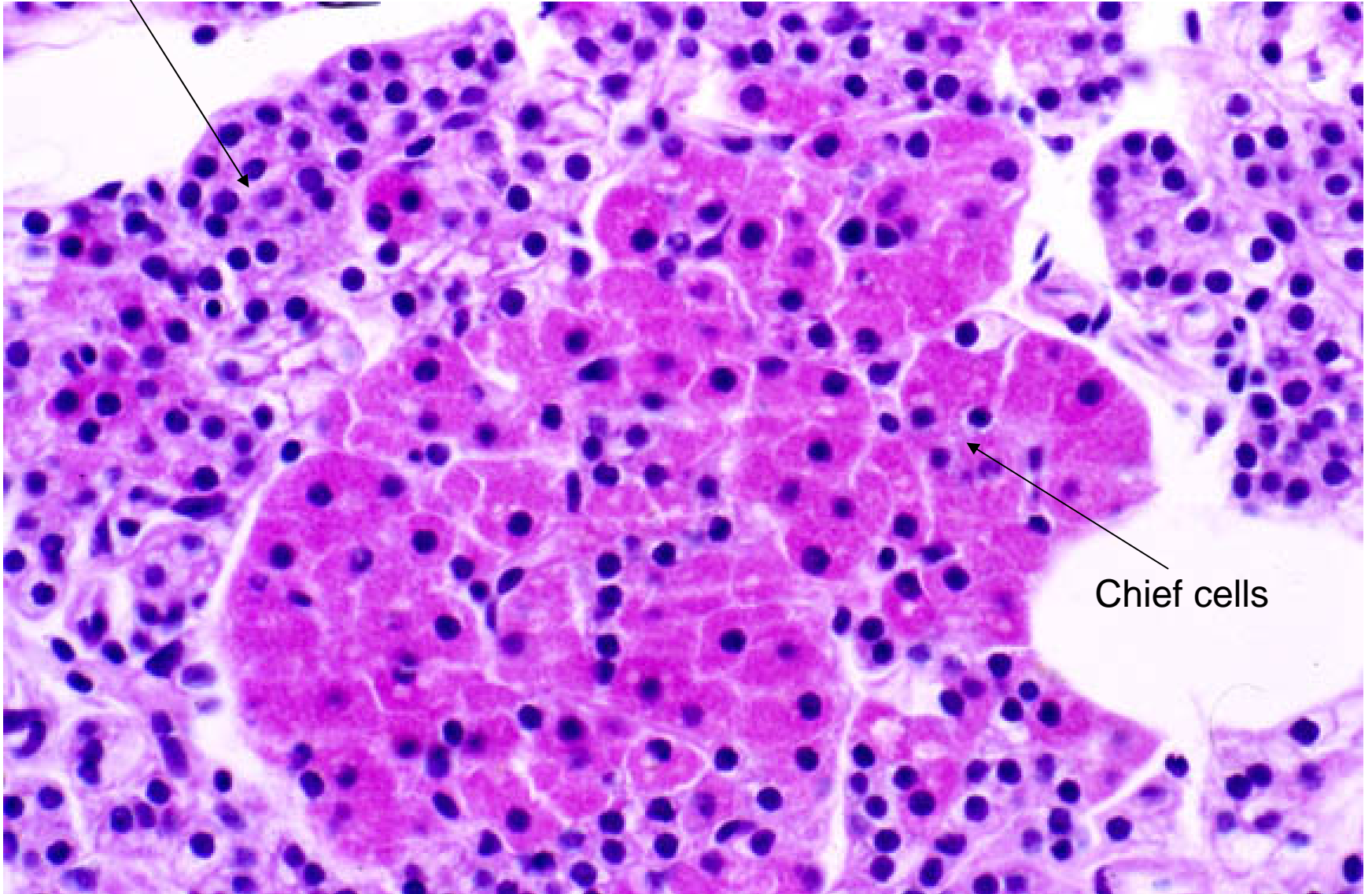
Parathyroid Gland

- Embedded in the posterior surface of the lateral lobe of the thyroid gland
- Contain two types of cells
 - **Chief (principal cells) cells**- produce parathyroid hormone (PTH, parathormone)
 - **Oxyphil cell** – function unknown



Parathyroid Gland

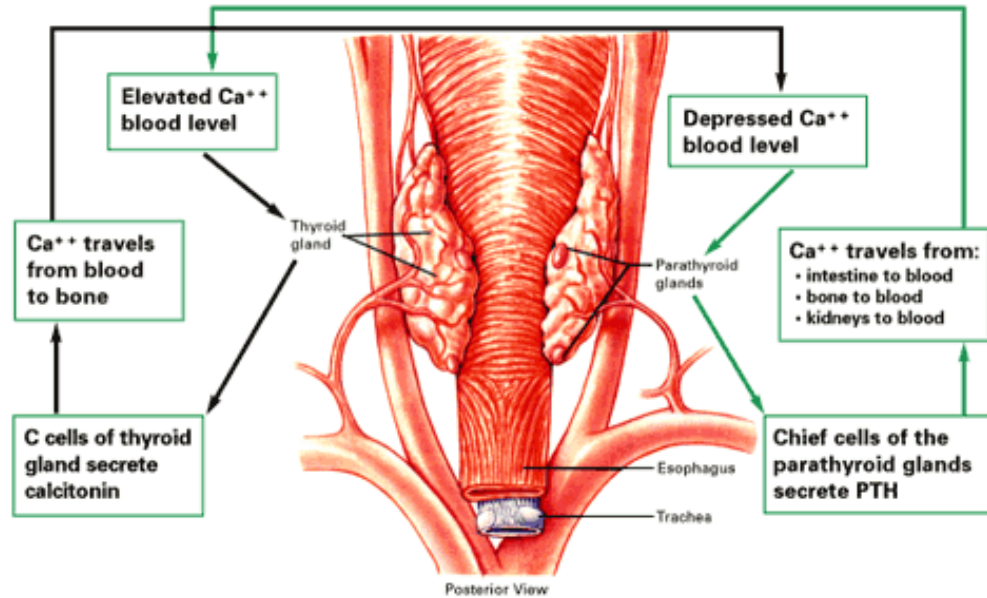
Oxyphil cells



Chief cells

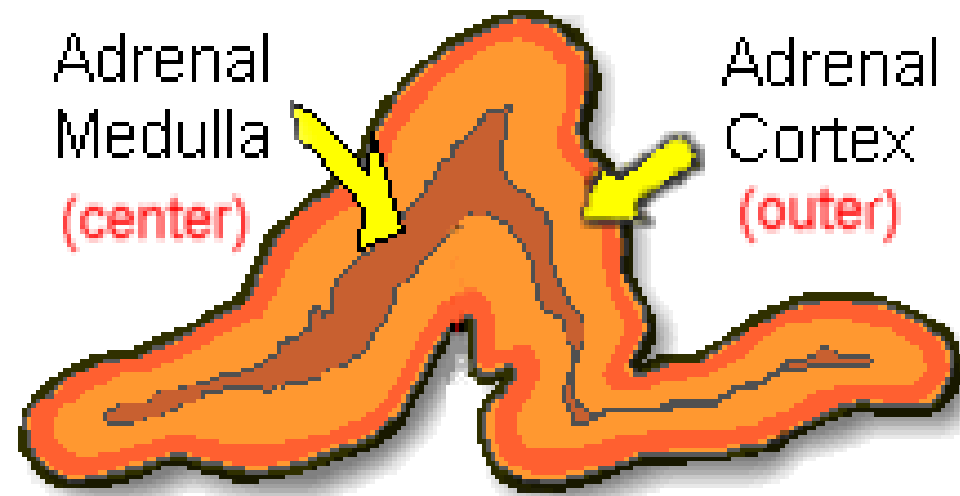
Parathyroid Hormone

- Low blood calcium stimulates chief cells to release PTH
- PTH promotes resorption of bone matrix by increasing osteoclast activity, which release calcium into blood,
- Decreases kidney loss of calcium and magnesium in urine
- Increases loss of phosphate (HPO_4^{2-})
- Stimulates the kidney to synthesize calcitriol (active vitamin D)
- **Calcitriol** stimulates increased absorption of calcium and magnesium from the GI tract

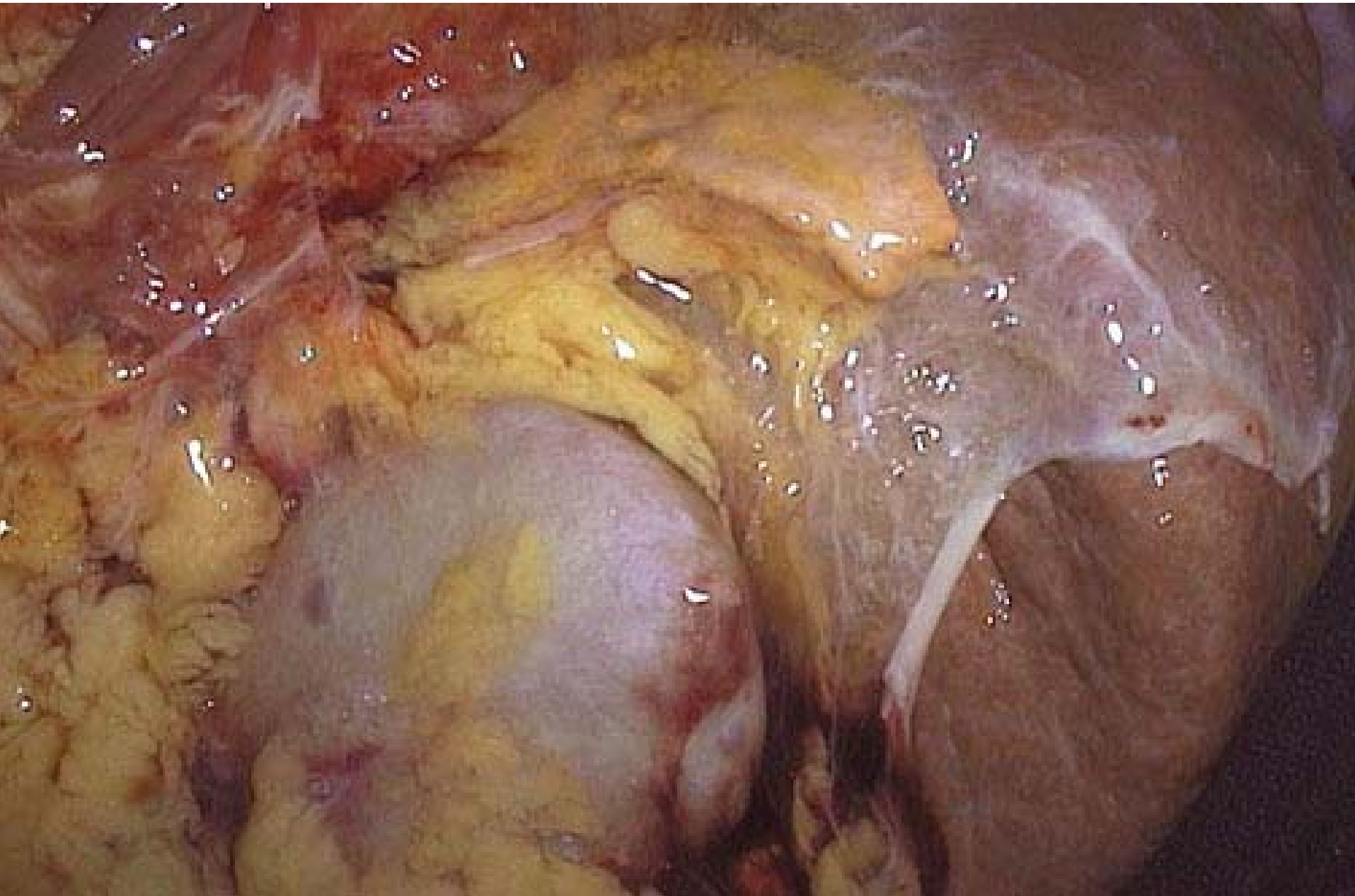


Adrenal Glands

- Also called suprarenal glands
- Sits like a cap on the superior pole of the kidney
- Consists of two parts with different origins and functions
 - adrenal medulla
 - adrenal cortex



Adrenal Gland

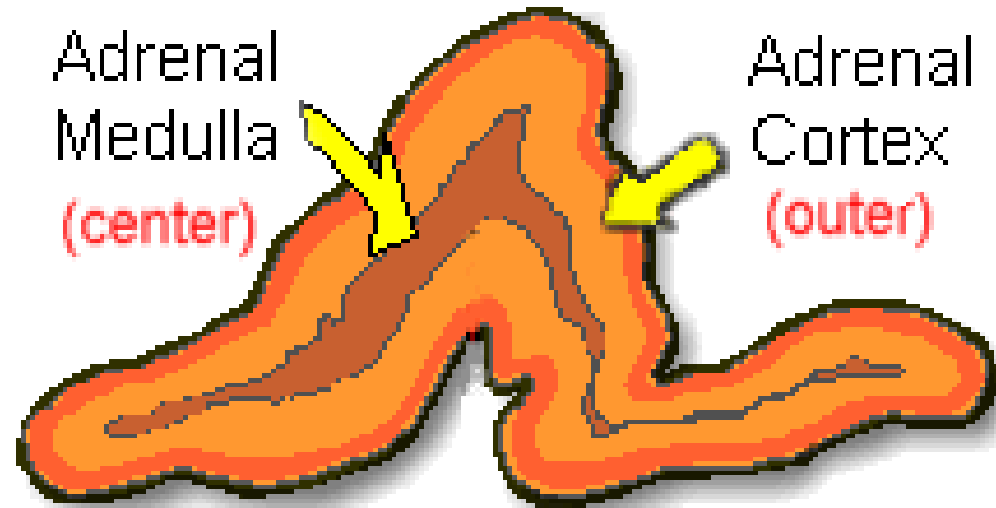


Sectioning across the adrenals reveals a golden yellow outer cortex and an inner red to grey medulla.



Adrenal Medulla

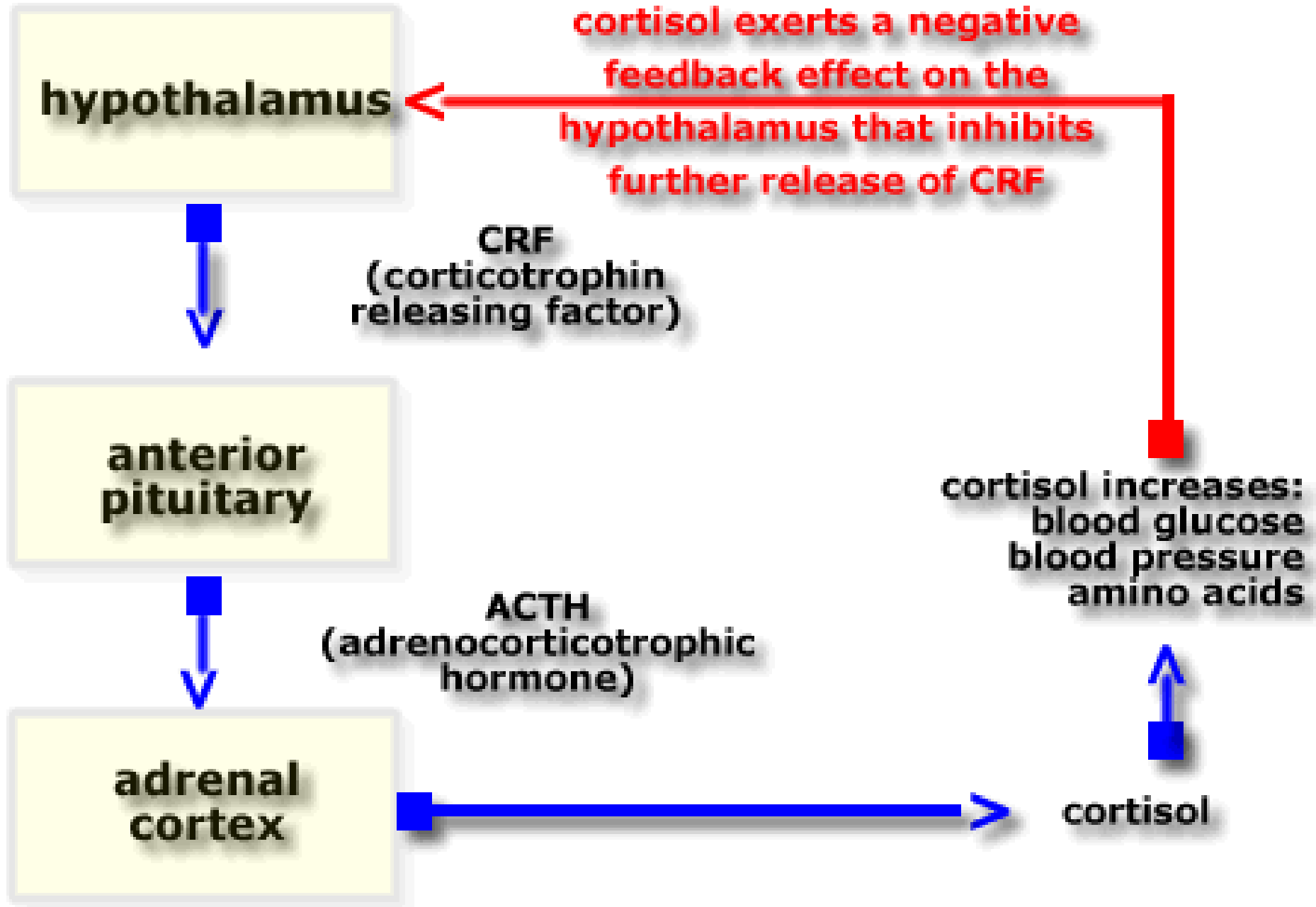
- Not fully formed until age 3
- Is a sympathetic ganglion consisting of modified neurons called **chromaffin cells** that lack dendrites and axons.
- These cells are richly innervated by preganglionic fibers
- Stimulation causes the secretion of catecholamines, especially epinephrine (3/4 of the output) and norepinephrine



Adrenal Medulla

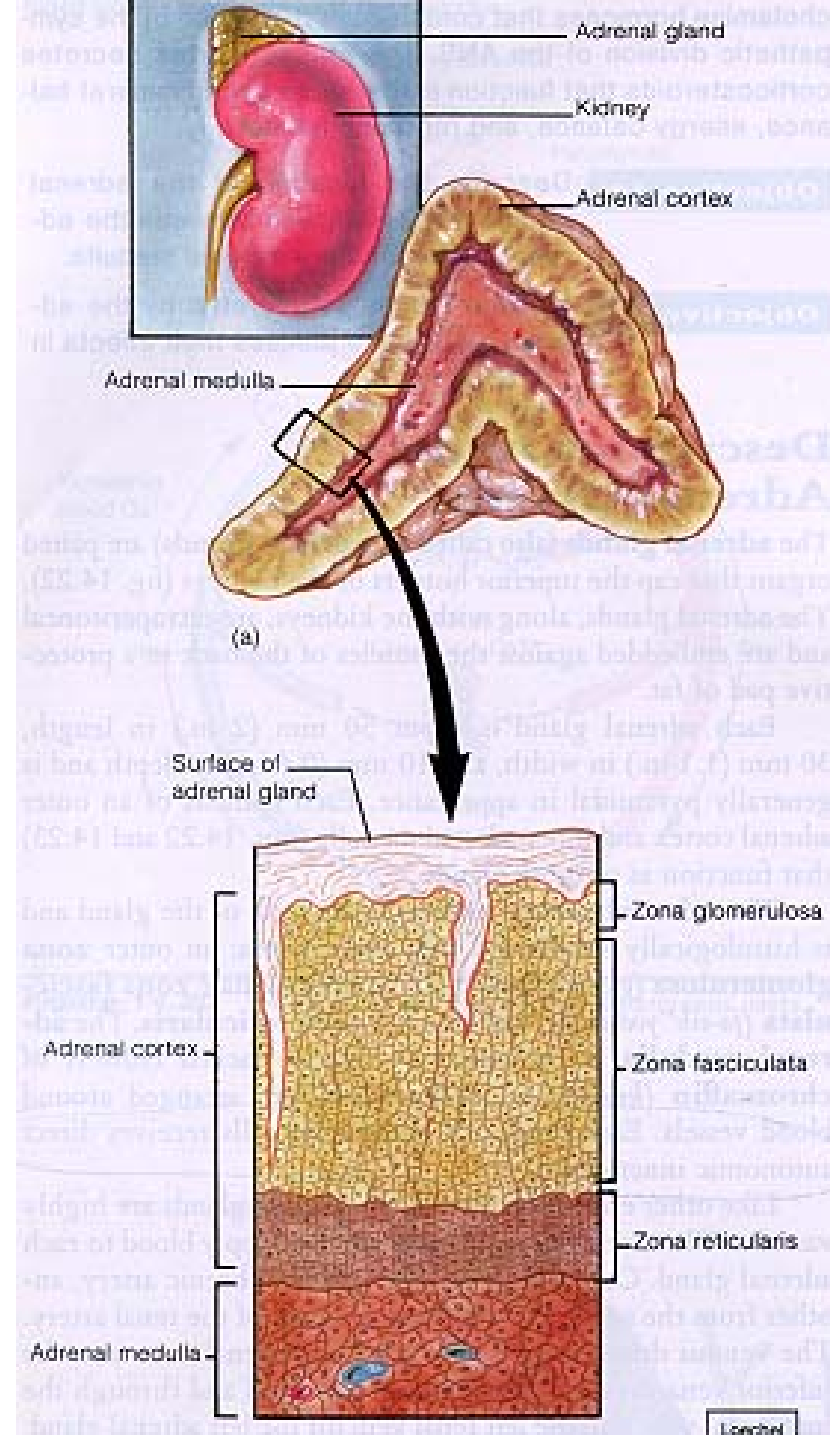
- Hormones supplement the effects of the sympathetic nervous system
- Effects last much longer than NS because the hormones circulate in the blood.
- They prepare the body for physical activity
 - raise the blood pressure and heart rate
 - increase circulation to the skeletal muscles
 - increase pulmonary airflow
 - Raises blood sugar by
 - **stimulate glycogenolysis** (hydrolysis of glycogen to glucose)
 - **stimulate gluconeogenesis** (the synthesis of glucose from amino acids and other substrates)
 - insures adequate glucose to the brain by
 - epiniphrine **inhibits insulin secretion** and thus, inhibits the use of glucose by the muscles and other insulin dependent organs (**glucose sparing effects**)

The Pituitary-Adrenal-Axis



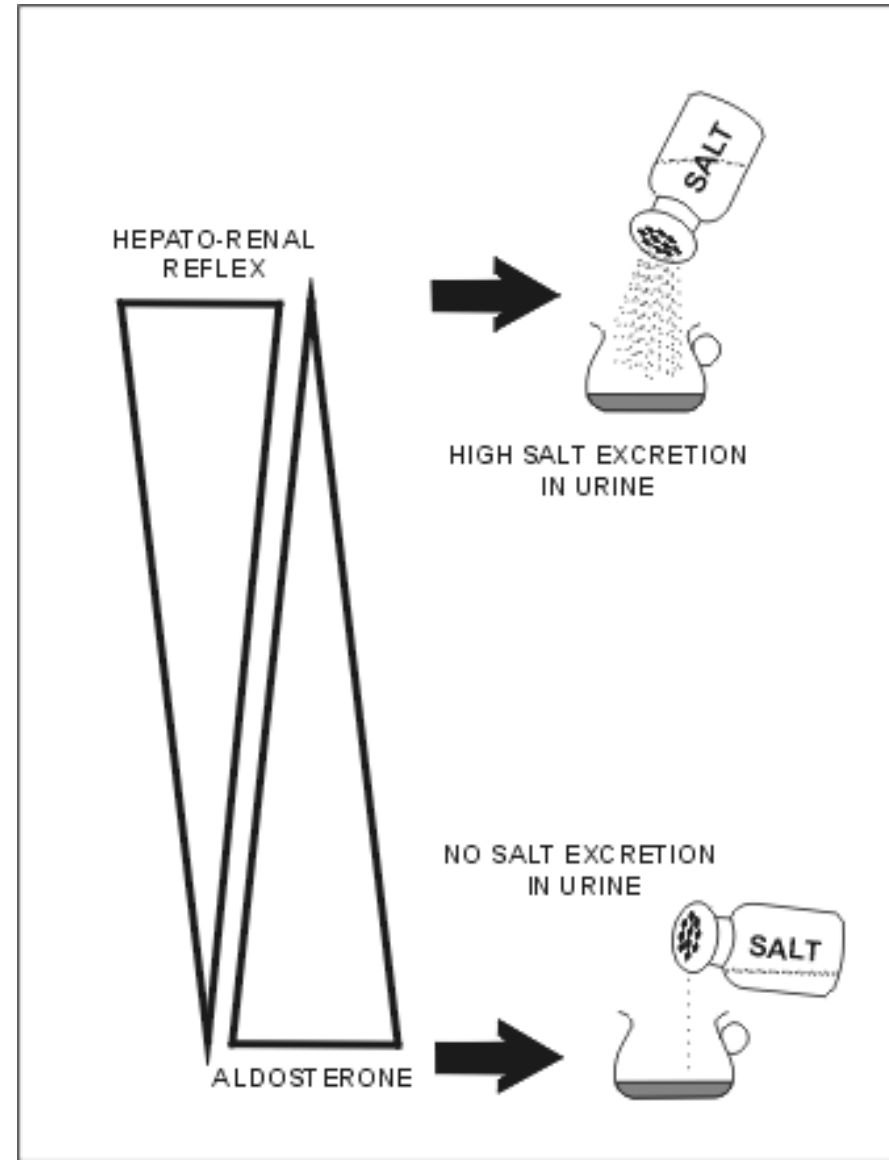
Adrenal Cortex

- Has 3 layers of glandular tissue
 - outer **zona glomerulosa**
 - middle **zona fasciculata**
 - Inner **zona reticularis**
- Cortex synthesizes more than 25 steroid hormones known collectively as the **corticosteroids** or **corticoids**



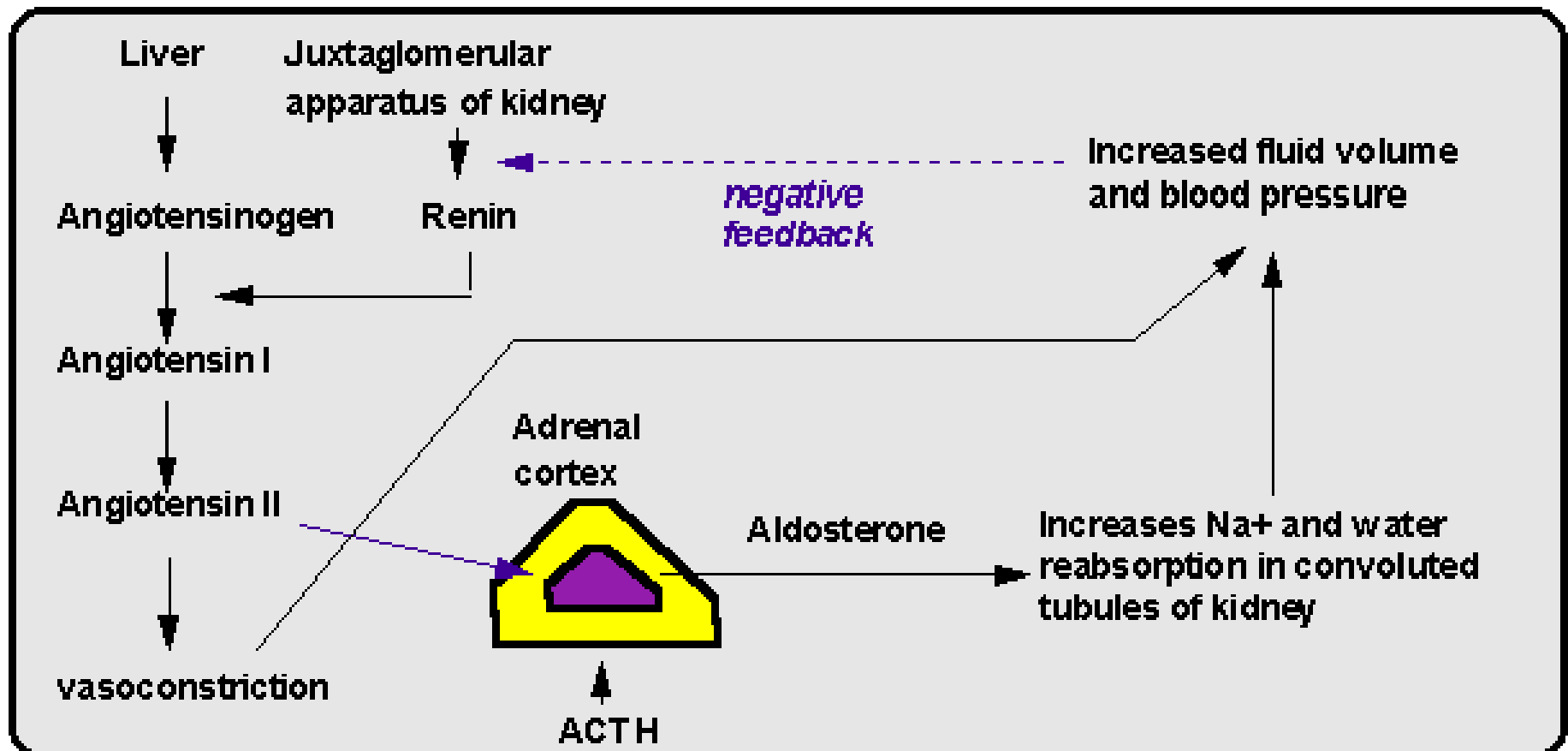
Adrenal Cortex: Zona glomerulosa

- secretes **mineralocorticoids**- act on the kidney to control electrolyte balance
- **Aldosterone**- the principal mineralcorticoid
 - promotes Na^+ retention and K^+ excretion by the kidney



Adrenal Mineralocorticoids

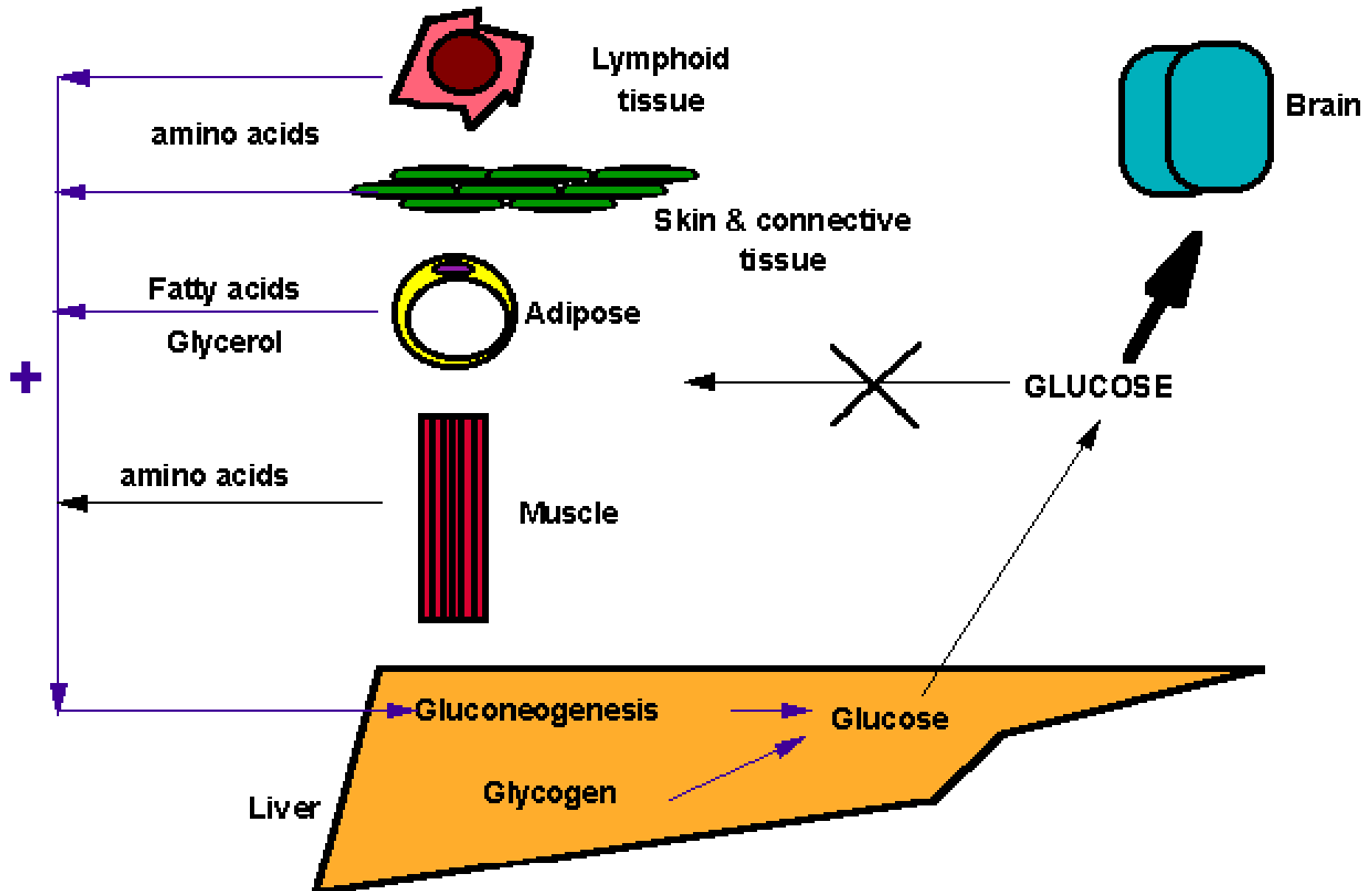
- Aldosterone is the major form;
- It controls body fluid volume by increasing sodium reabsorption by kidneys;
- Aldosterone secretion is stimulated by:
 - mainly by the activation of renin-angiotensin system in response to decreased blood pressure, low plasma sodium and high plasma potassium;
 - ACTH has a minor role.



Adrenal Cortex: Zona fasciculata

- Secretes **glucocorticoids**, especially cortisol (hydrocortisone) and corticosterone, a less potent relative
- actions of glucocorticoids
 - stimulate fat and protein catabolism
 - gluconeogenesis
 - the release of fatty acids and glucose into the blood
- all helps to adapt the body to stress and repair damaged tissues
- Other effects
 - have an antiinflammatory effects
 - long term secretion suppresses the immune system

Glucocorticoid actions



Adrenal Cortex: Zona Reticularis

Secretes sex steroids including

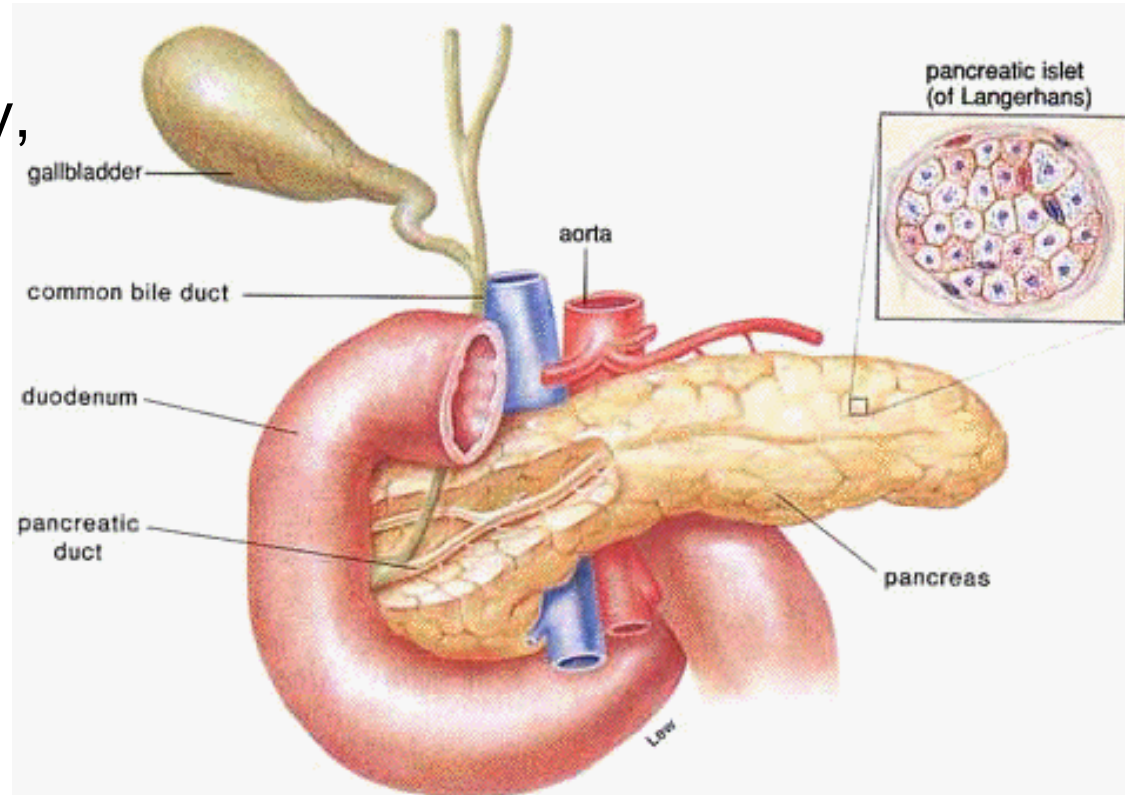
- weak androgens which control many aspects of male development and reproductive physiology
 - **dehydroepiandrosterone (DHEA)**- the principal androgen
 - has weak hormonal effects in its self
 - converted to the more potent androgen, testosterone, by other tissue
 - is a minor contributor of testosterone in men because of the testicles which produces so much more
 - in women the adrenal gland meets 50% of the total androgen required
 - acts to stimulate the development of pubic and axillary hair and apocrine scent glands at puberty and sustains the libido throughout adult life

Adrenal Cortex: Zona Reticularis

- Smaller amount of estrogens (estradiol)
- is of minor importance in women of reproductive age because of its small quantity compared to estrogen from the ovaries
- After menopause it is the only remaining estrogen source
- Both androgens and estrogens promote adolescent growth and help to sustain bone mass.

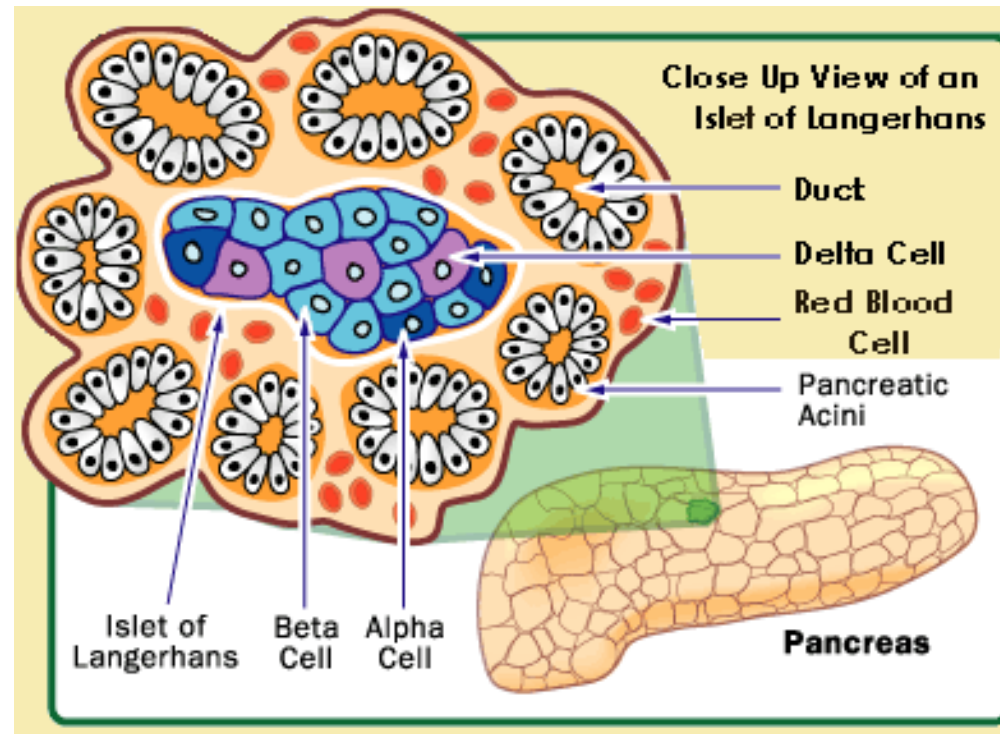
The Pancreas

- Located retroperitoneally, inferior and dorsal to the stomach
- Most of the pancreas is an exocrine digestive gland
- has scattered endocrine tissue called pancreatic islets (**islets of Langerhans**)
 - Constitutes only 2% of the pancreatic tissue

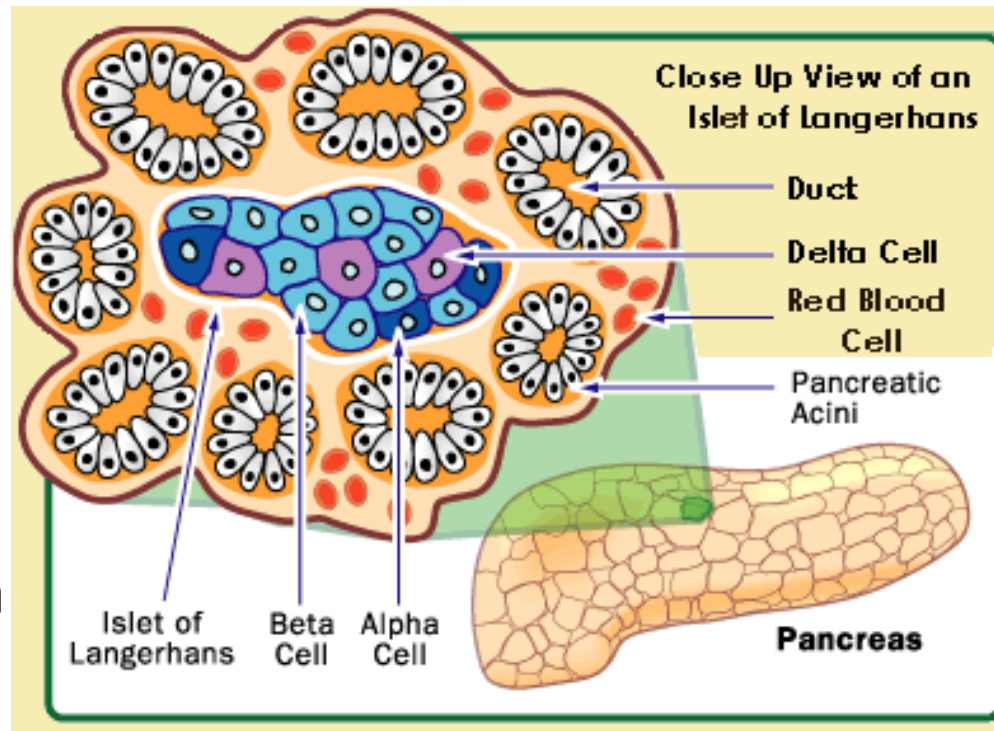


The islets secrete

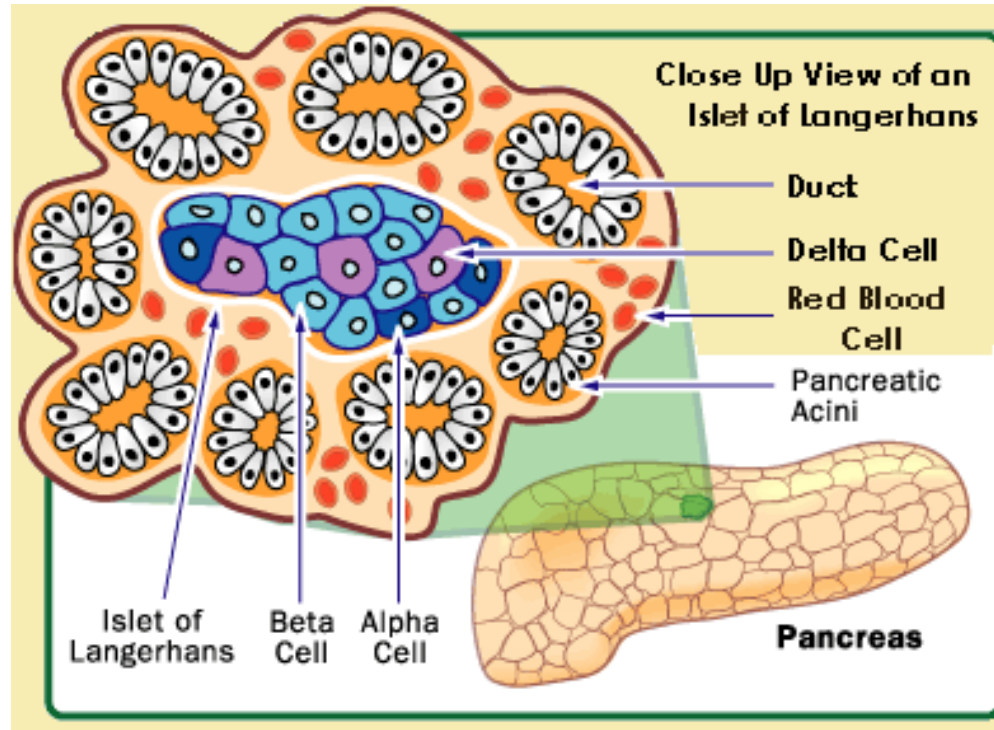
- **insulin**- secreted by beta cells of the islets
 - stimulates the cells to absorb glucose and amino acids
 - stimulates muscles and adipose to store glycogen and fat.
 - promotes liver synthesis of glycogen
 - antagonizes the effects of glucagon



- **Glucagon**- secreted by alpha cells when blood glucose falls
- in the liver it stimulates gluconeogenesis, glycogenolysis, and the release of glucose into circulation
- In adipose tissue, it stimulates fat catabolism and the release of free fatty acids into circulation
- secreted in response to rising amino acid levels after a high protein meal and promotes amino acid absorption and uptake for gluconeogenesis



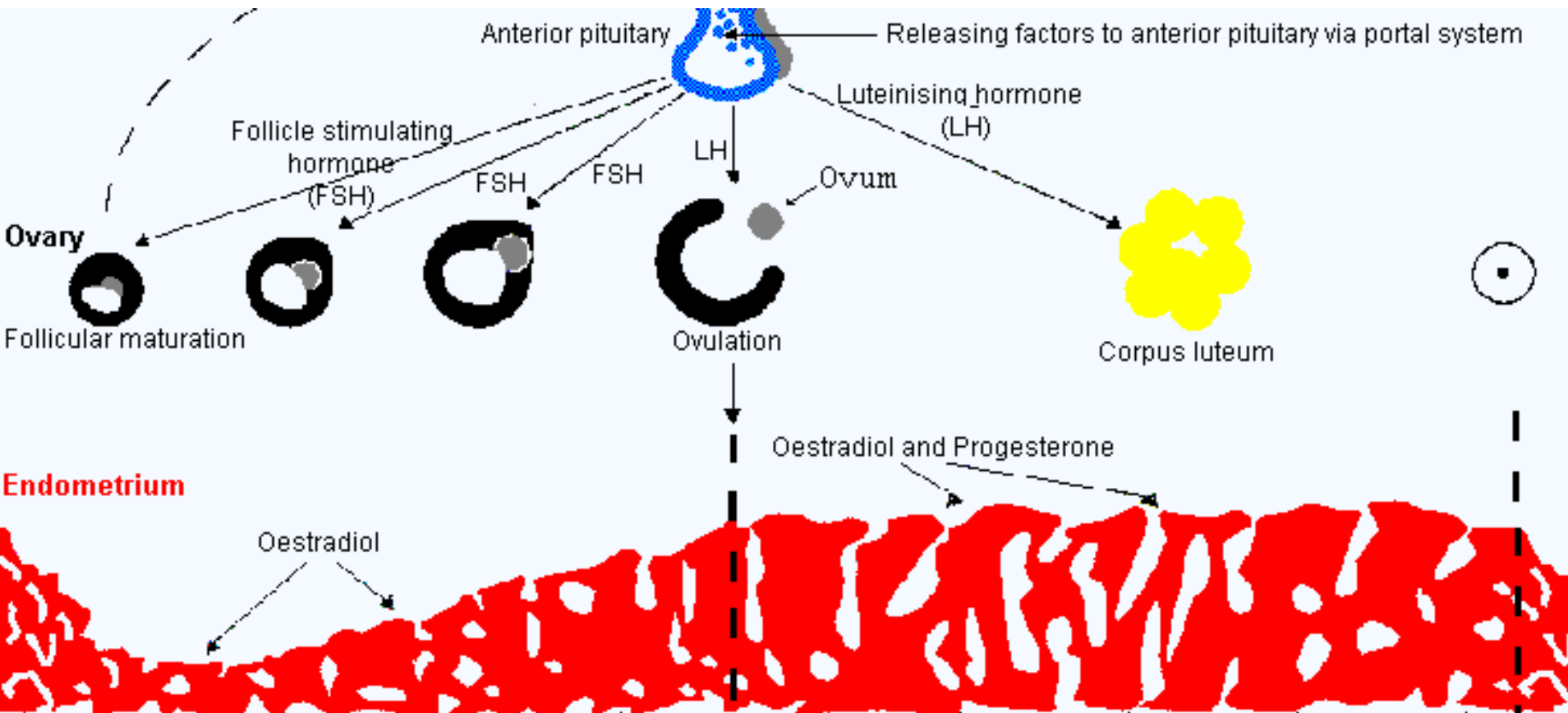
- **Somatostatin**- secreted by the delta cells when blood glucose and amino acids rise after a meal
- has an endocrine effect that inhibits various digestive functions
- Acts as a paracrine to inhibit the secretion of glucagon and insulin by the neighboring alpha and beta cells
- Any hormone that raises blood glucose concentration is called a **hyperglycemic hormone**
- Any hormone that lowers blood glucose is a **hypoglycemic** (insulin)



Gonads

- are both endocrine and exocrine
- Exocrine products are eggs and sperm
- Endocrine products are the gonadal hormones, most of which are steroids

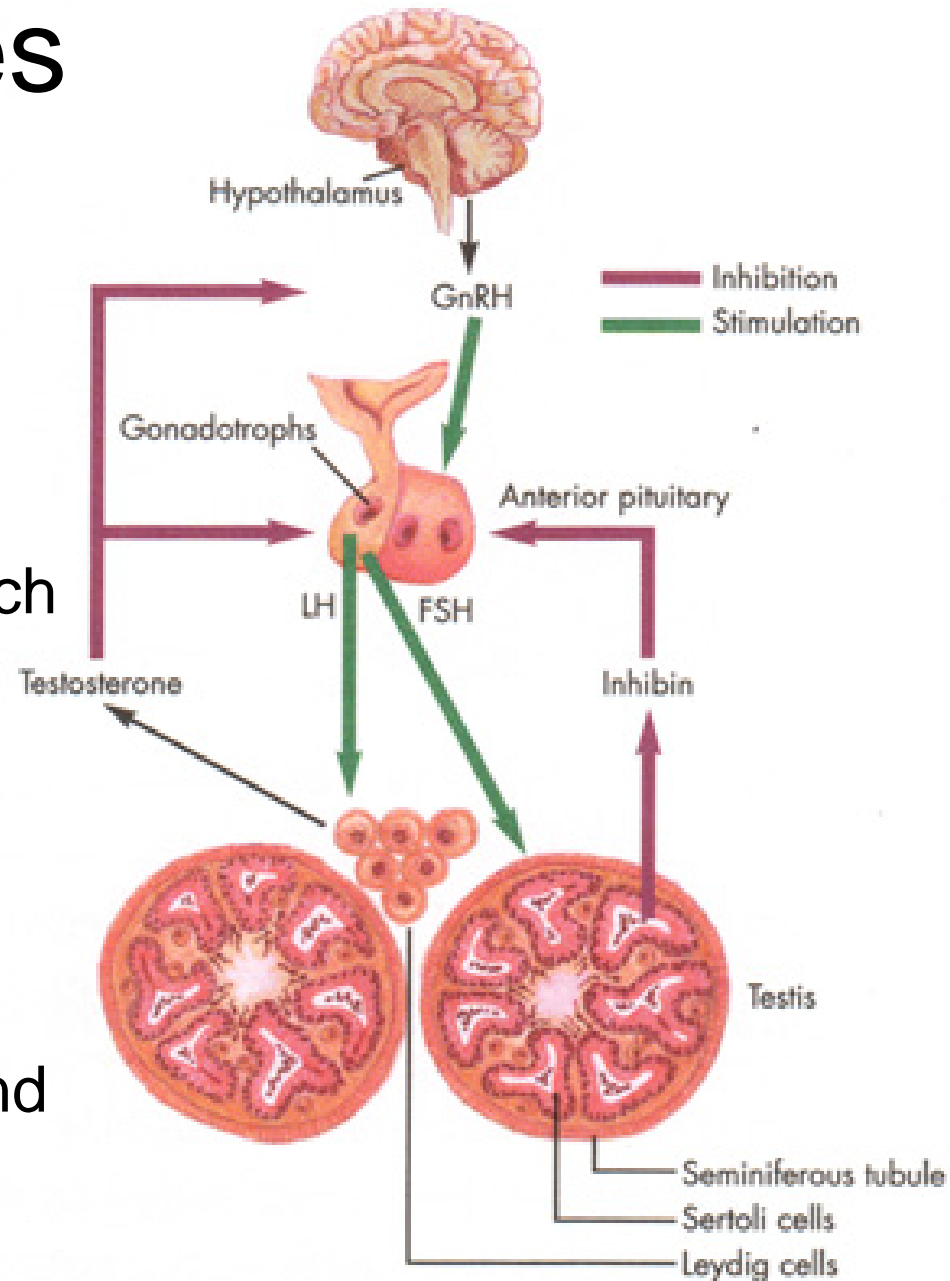
Gonads: Ovaries



- The **ovaries** contains an egg cell surrounded by a wall of granulosa cells
- **granulosa cells** produce and estrogen called **estradiol**
 - after ovulation the cells left behind are called the **corpus luteum** which secretes estradiol and progesterone for up to 12 days or 8 to 12 weeks in the event of pregnancy.
 - also secrete **inhibin** which suppresses FSH secretion by means of negative feedback of the ant. pit.

Gonads: Testes

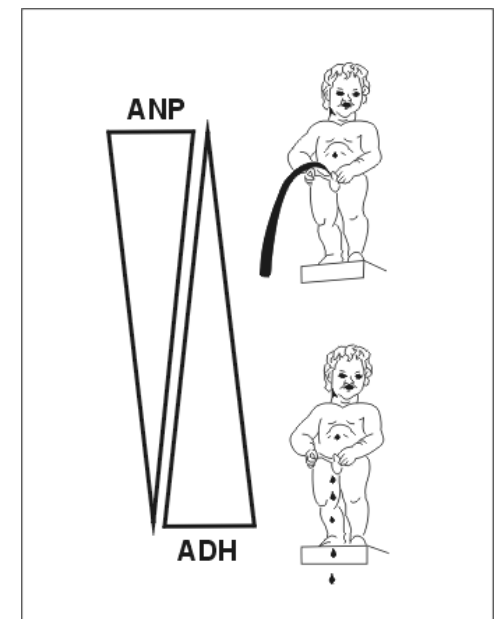
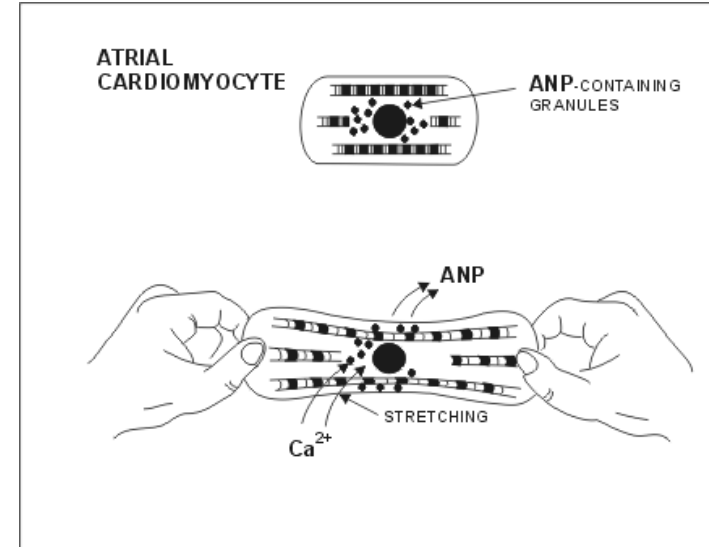
- Testes consists of mainly of microscopic **seminiferous tubes** that **produce sperm**.
- Nestled between them are clusters of cells called **interstitial (Leydig) cells** which **produce testosterone** and lesser amounts of weaker androgens and estrogens
- Also have **sustentacular (Sertoli cells) cells** which secrete **inhibin**, which **suppresses FSH** secretion and stabilize the rate of sperm production



Endocrine Functions of Other Organs

Heart

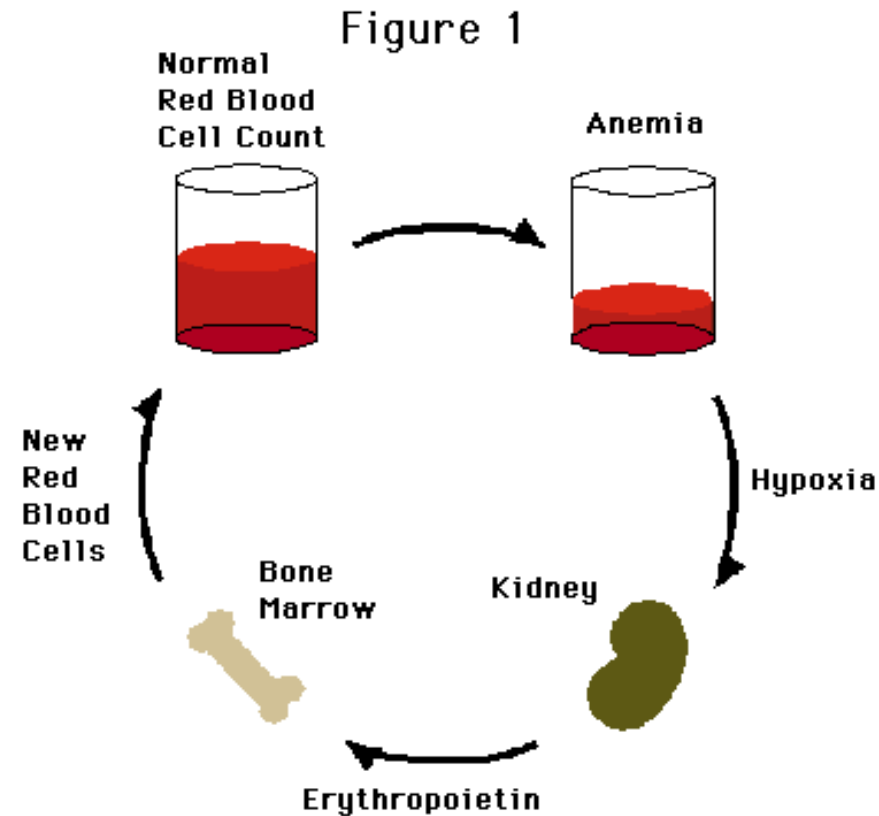
- secretes **atrial natriuretic peptide (ANP)** upon stretching of heart muscle by increased pressures
 - ANP increases sodium excretion and urine output and opposes the action of angiotensin II
 - In effect, lowering blood pressure



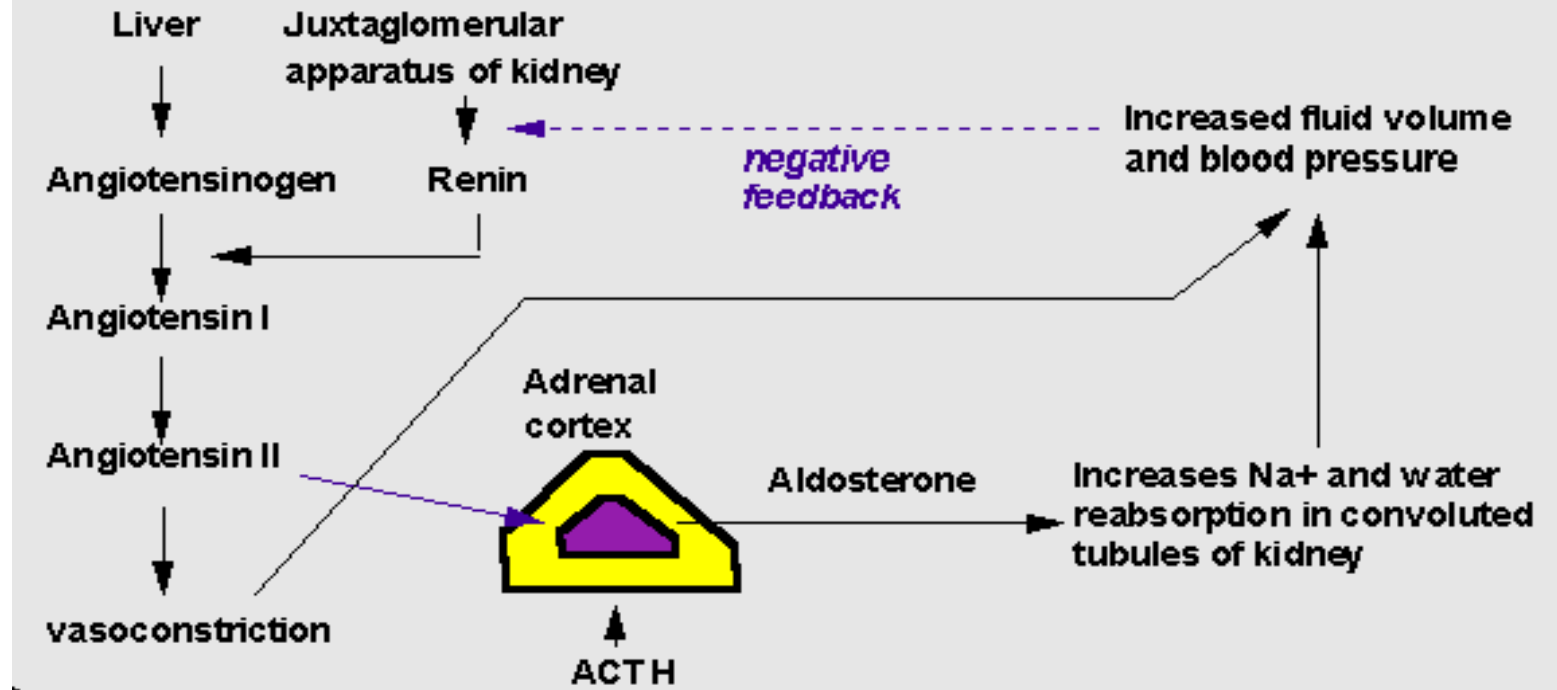
Endocrine Functions of Other Organs

Kidneys

- produces 85% of the body's **erythropoietin (EPO)**, a hormone that stimulates the bone marrow to produce red blood cells
- converts the vitamin D precursor, 25-hydroxy vitamin D3 to its active form, 1,25-dihydroxy vitamin D3



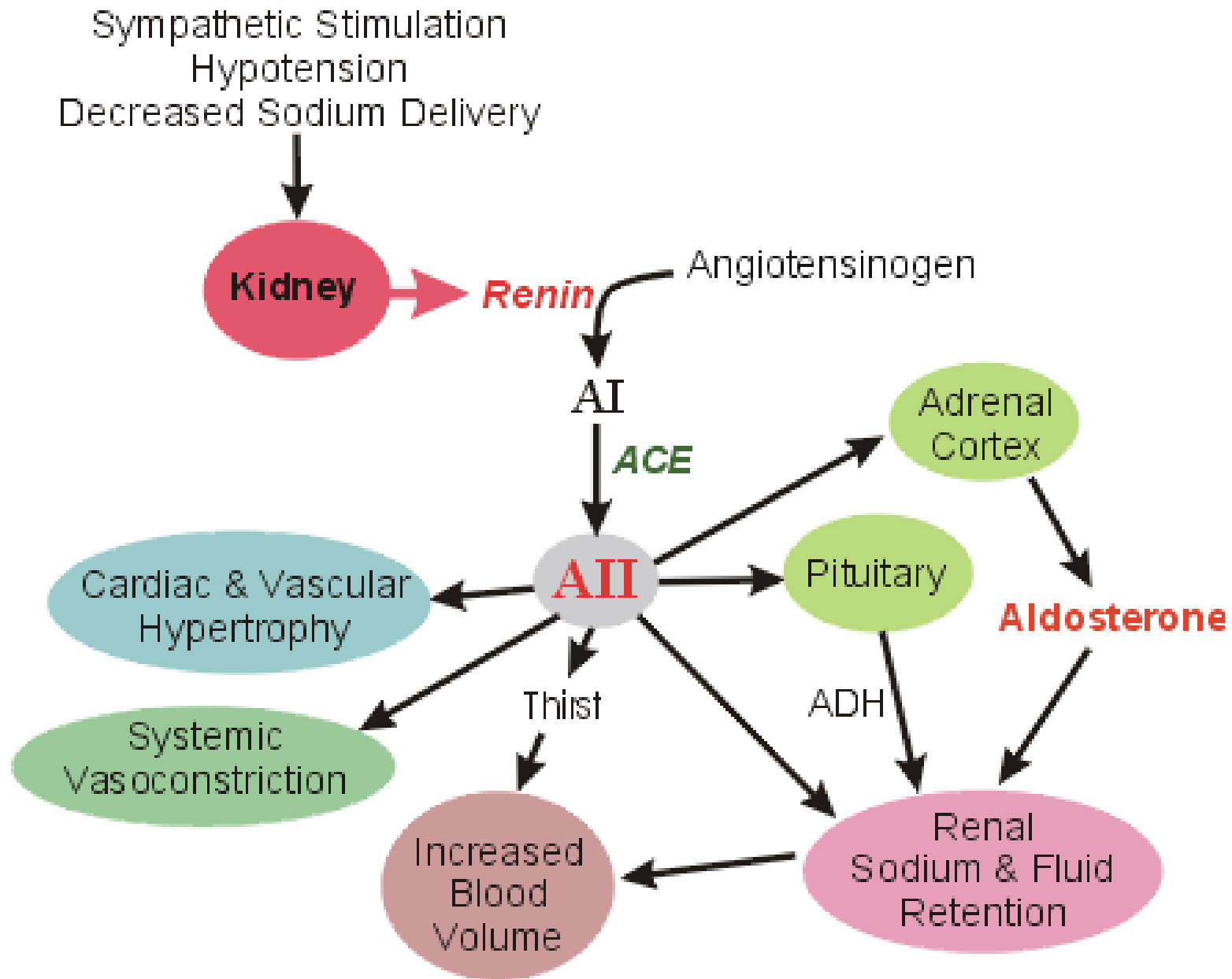
Stimulus: Hypoxia due to decreased RBC count, decreased availability of O_2 to blood, or increased tissue demands for O_2



Liver

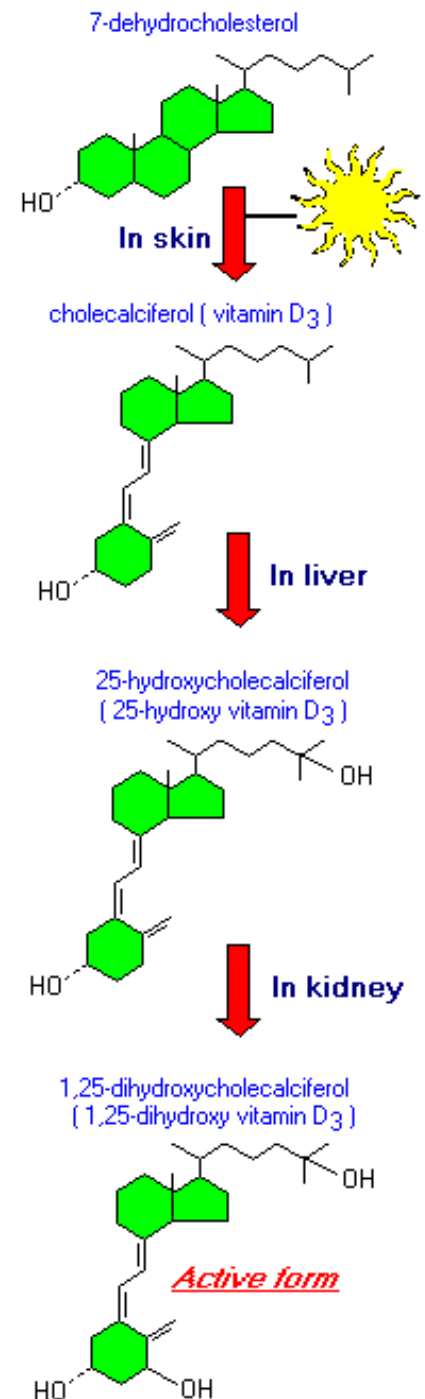
- secretes a hormone precursor called **angiotensinogen** which is converted to **angiotensin I** the kidney enzyme, **renin**.
- Angiotensin I is converted to **angiotensin II** by the lung enzyme, **angiotensin-converting enzyme (ACE)**
- ACE is a hormone that stimulates vasoconstriction and aldosterone secretion
- Overall effect is to raise blood pressure
- The liver is also a source of IGF-I which mediates the action of growth hormone
- It secretes about 15% of the body's **erythropoietin**.

Actions of Angiotensin II

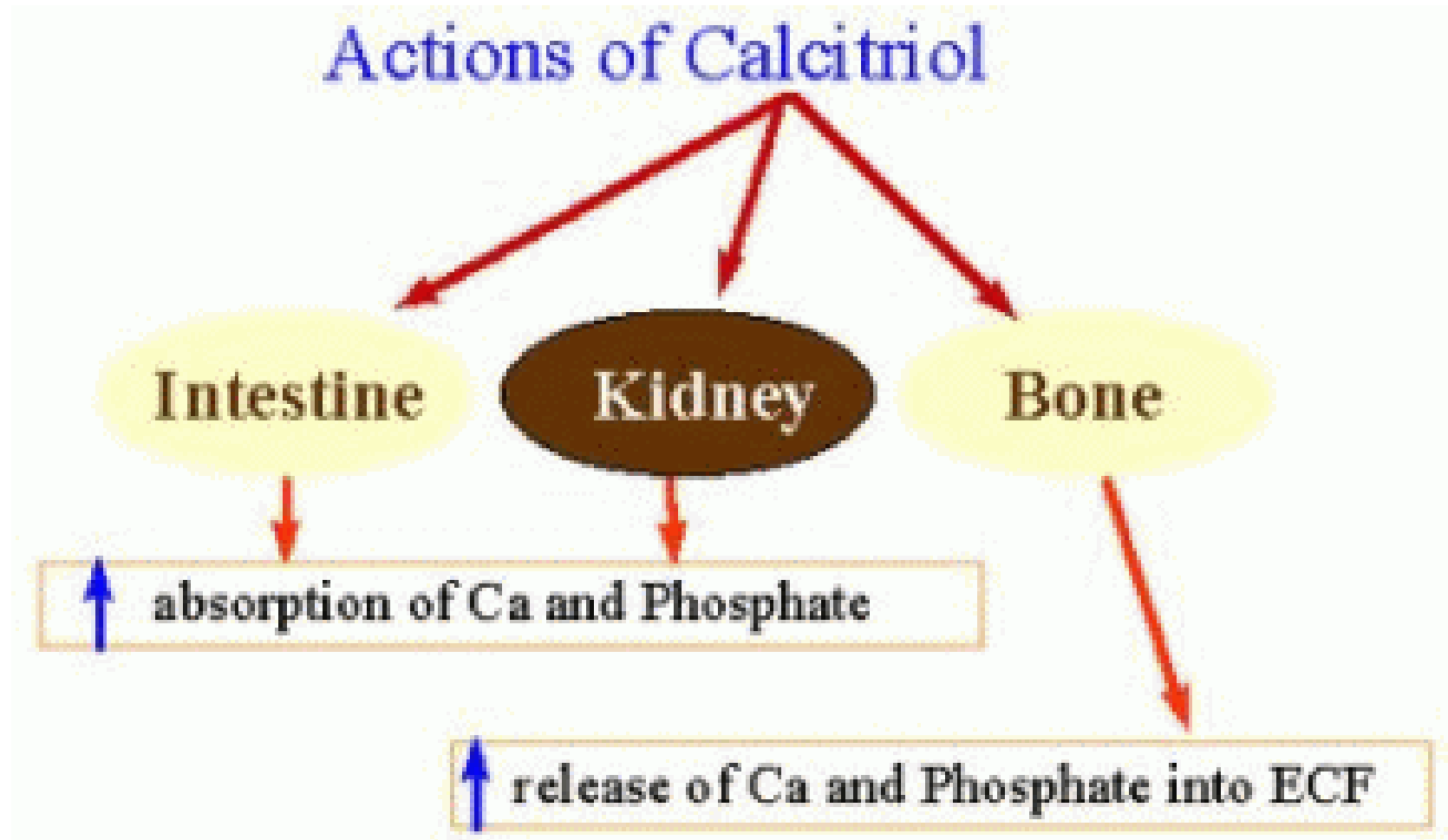


Skin

- Keratinocytes of the epidermis produce vitamin D3, the first step in the synthesis of calcitriol.
- The liver converts vitamin D3 to another precursor, 25-hydroxy vitamin D3.
- The kidney 25-hydroxy vitamin D3 to the active form, calcitriol (1,25 dihydroxy vitamin D3)



Actions of Calcitriol: Active Vit. D



Mechanisms of Hormone Action

- Hormones only stimulate those cells that have receptors for them
- The receptors may be located on the plasma membrane, on mitochondria and other organelles in the cytoplasm, or in the nucleus.
- The receptors act as switches to turn certain metabolic pathways on or off when the hormone binds to them
- The target cell usually has a few thousand receptors for a given hormone

Mechanisms of Hormone Action

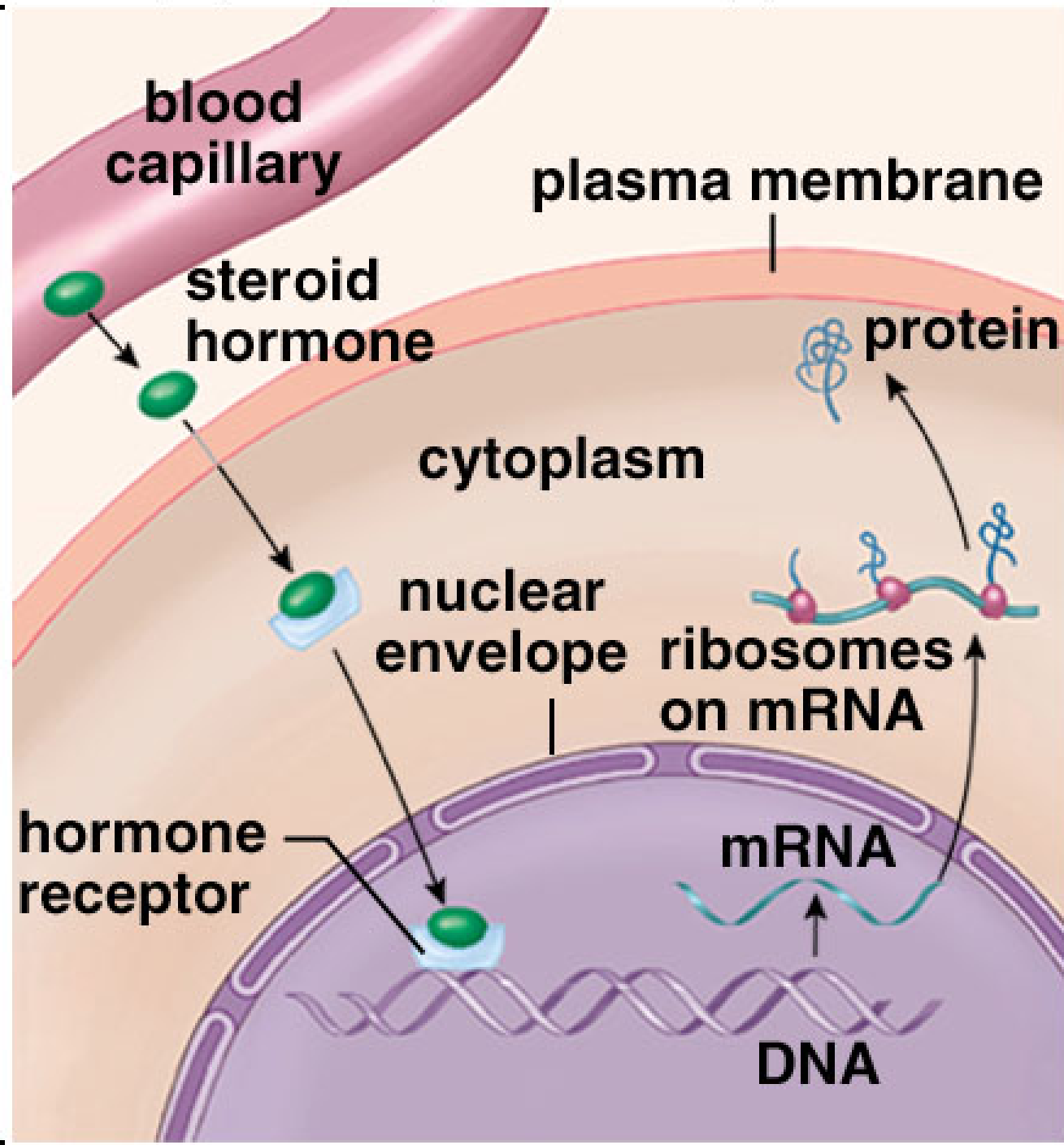
- Receptor-hormone interactions exhibit
 - **specificity**- meaning that the receptor for one hormone will not bind other hormones
 - **saturation**- the condition in which all the receptor molecules are occupied by hormone molecules, thus adding more hormone will not produce any greater effect.

Hydrophilic Hormones

- These hormones easily penetrate the phospholipid plasma membrane and enter the cytoplasm.
- They may enter the nucleus and bind to a receptor associated with the DNA
- The receptor has 3 functional regions that explain its actions on the DNA
 - one that binds the hormone
 - one that binds to an acceptor site on the chromatin
 - one that activates DNA transcription at that site
- Transcription produces new mRNA that leads to the synthesis of proteins, which then may alter the metabolism of the target cell

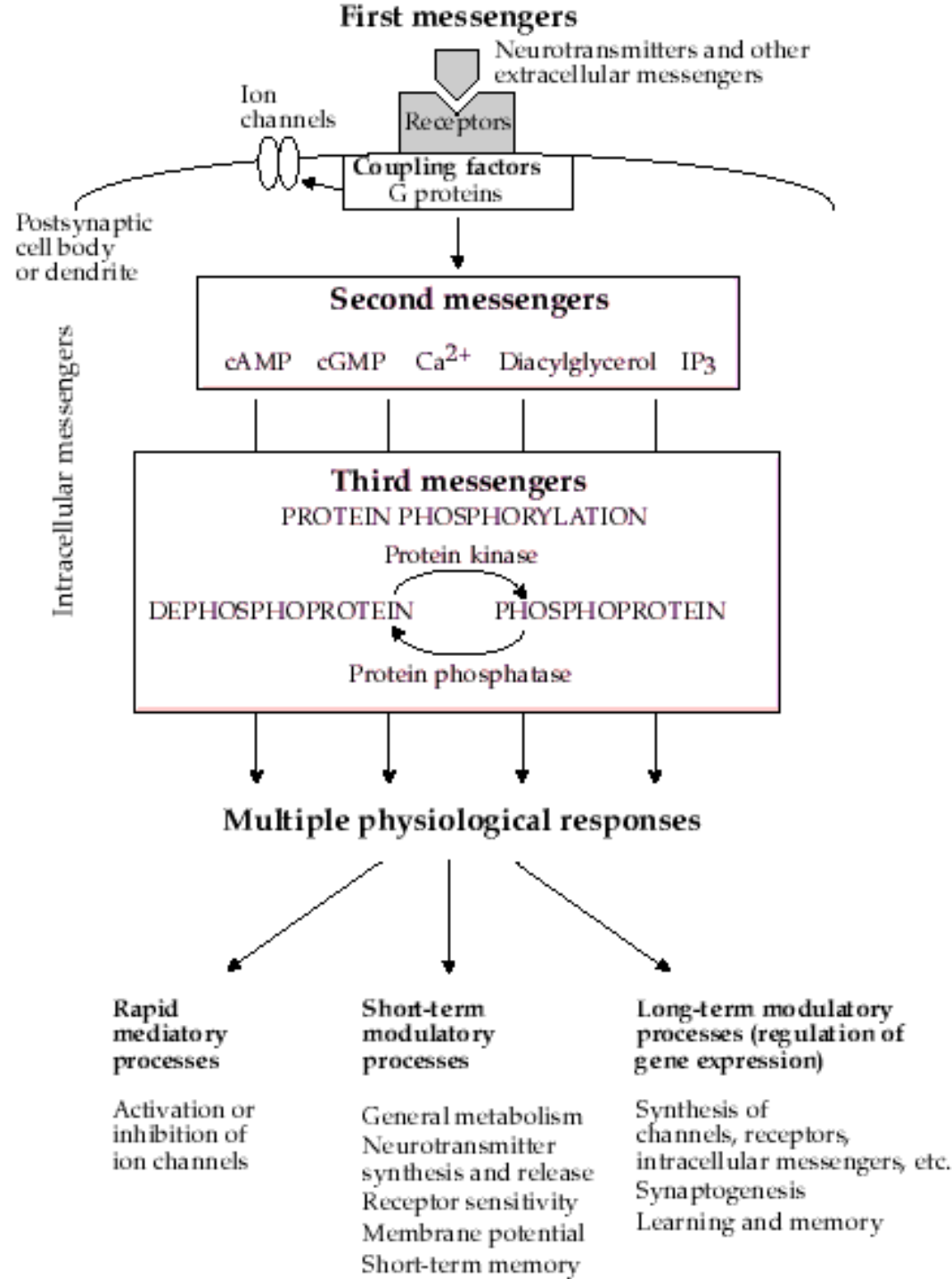
Cellular Activity of Hormones

Action of steroid hormone



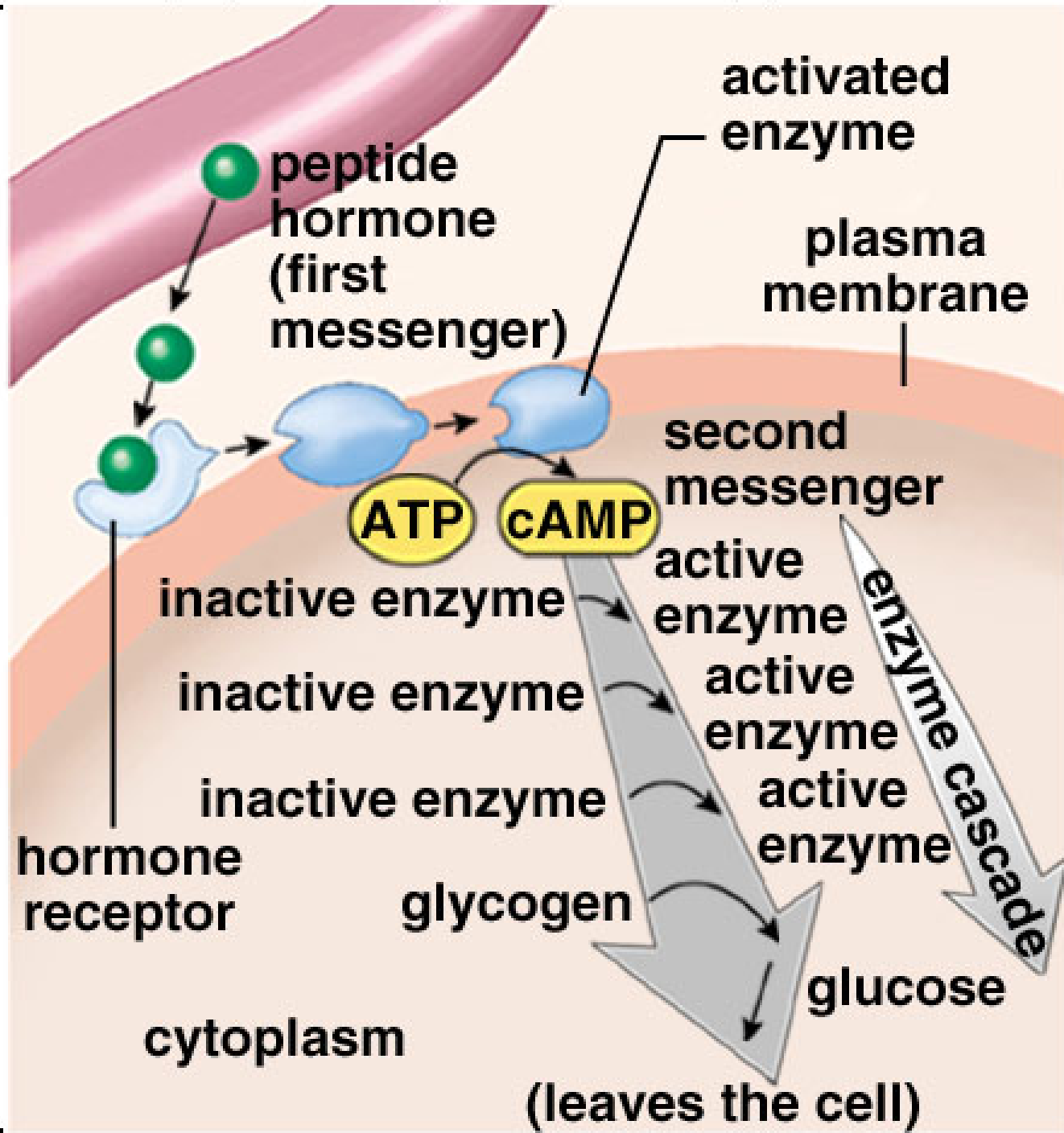
Mechanisms of Hormone Action

- Hydrophilic hormones cannot penetrate into a target cell, so they must exert their actions indirectly.
- Hormones bind to cell-surface receptors which are linked to **second-messengers systems** on the other side of the plasma membrane.

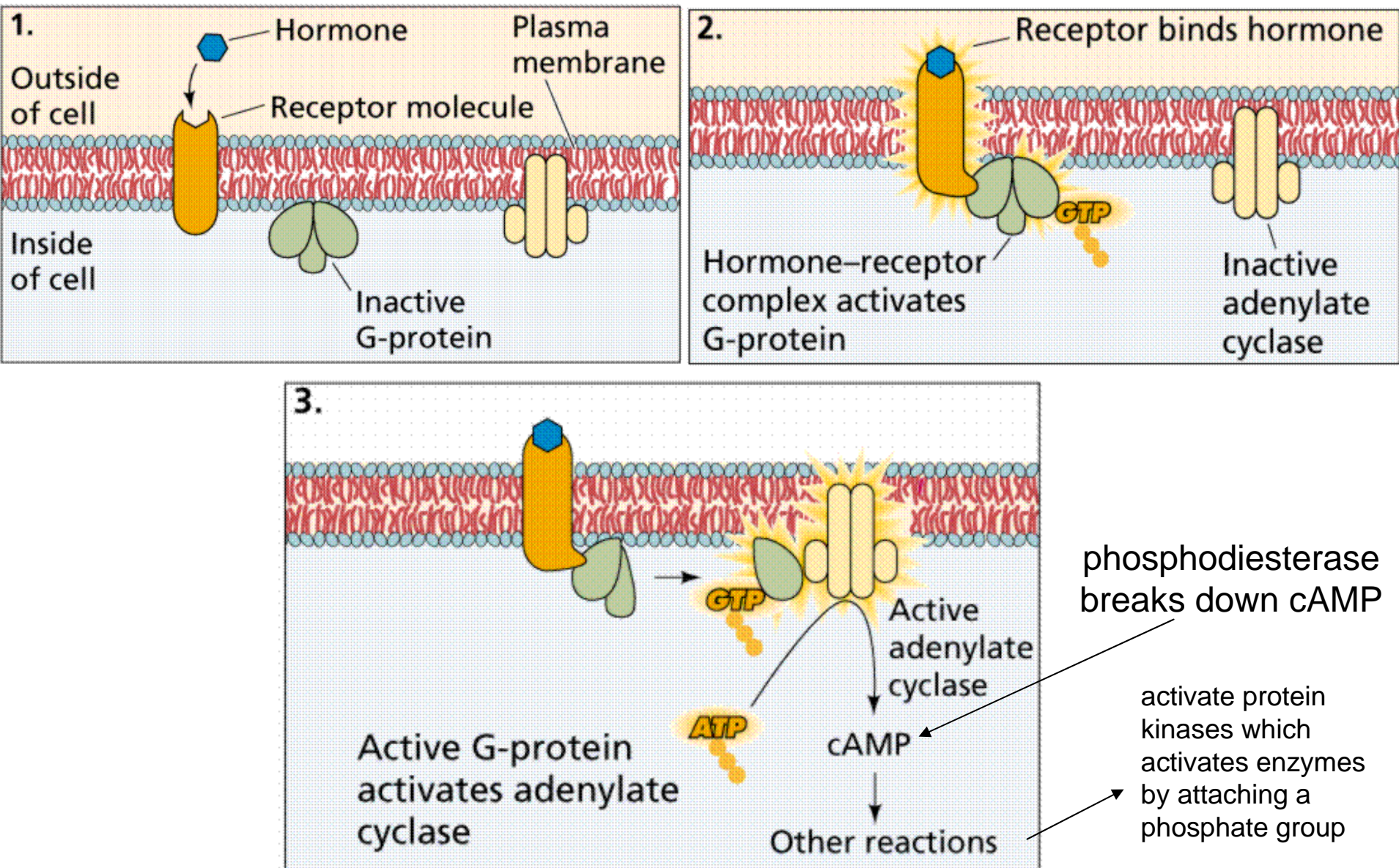


Cellular Activity of Hormones

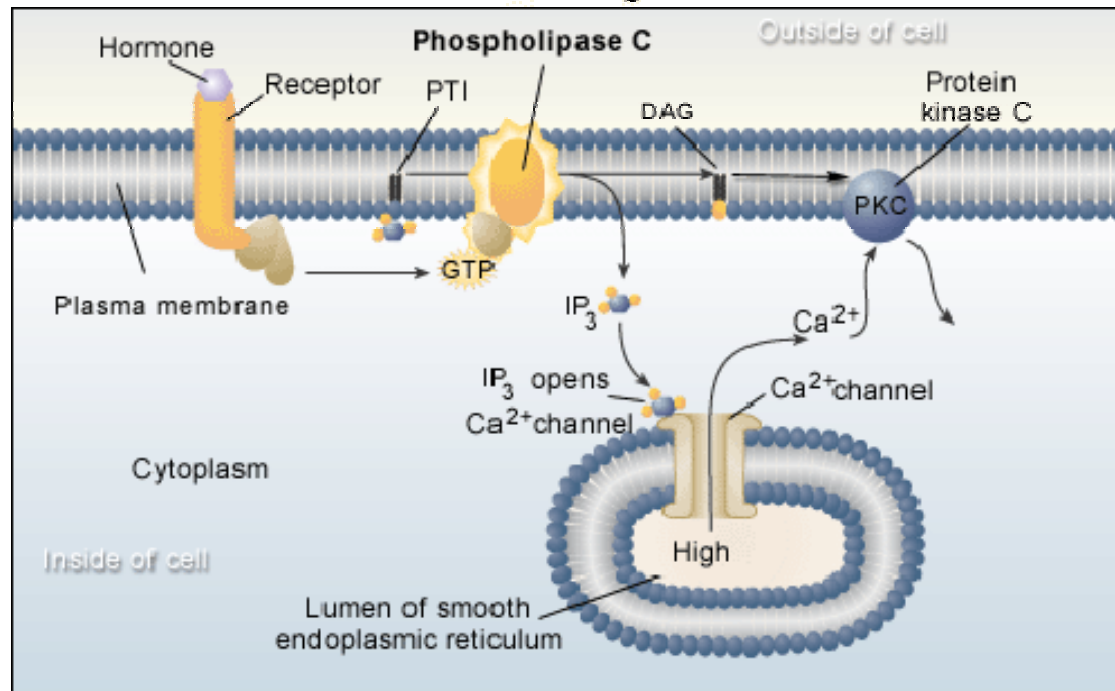
Action of peptide hormone



Second Messenger: Cyclic AMP



Second Messengers



Diacylglycerol (DG) and Inositol Triphosphate (IP₃) as a second messenger

- the binding of a hormone to a membrane receptor activates a G protein.
- The G protein activates a membrane enzyme, **phospholipase C**.
- Phospholipase breaks down membrane phospholipids into diacylglycerol and (IP₃)
- DG activates protein kinase
- IP₃ binds to gated calcium channels in the plasma membrane, admitting calcium to the cell from the ECF or it triggers calcium release from the smooth ER.
- Ca ions have a variety of effects: can open other ion channels in the plasma membrane, can function as a cofactor that activates enzymes, or can bind to **calmodulin**, a protein that activates protein kinases.
- Protein kinases exert the same variety of metabolic effects here as they do in the cAMP system.

Stress

- Defined as any situation that upsets homeostasis and threatens one's physical or emotional well-being.
- The body's reaction to stress is described as the stress response of the general adaptation syndrome (GAS)

Stress

Three stages of stress

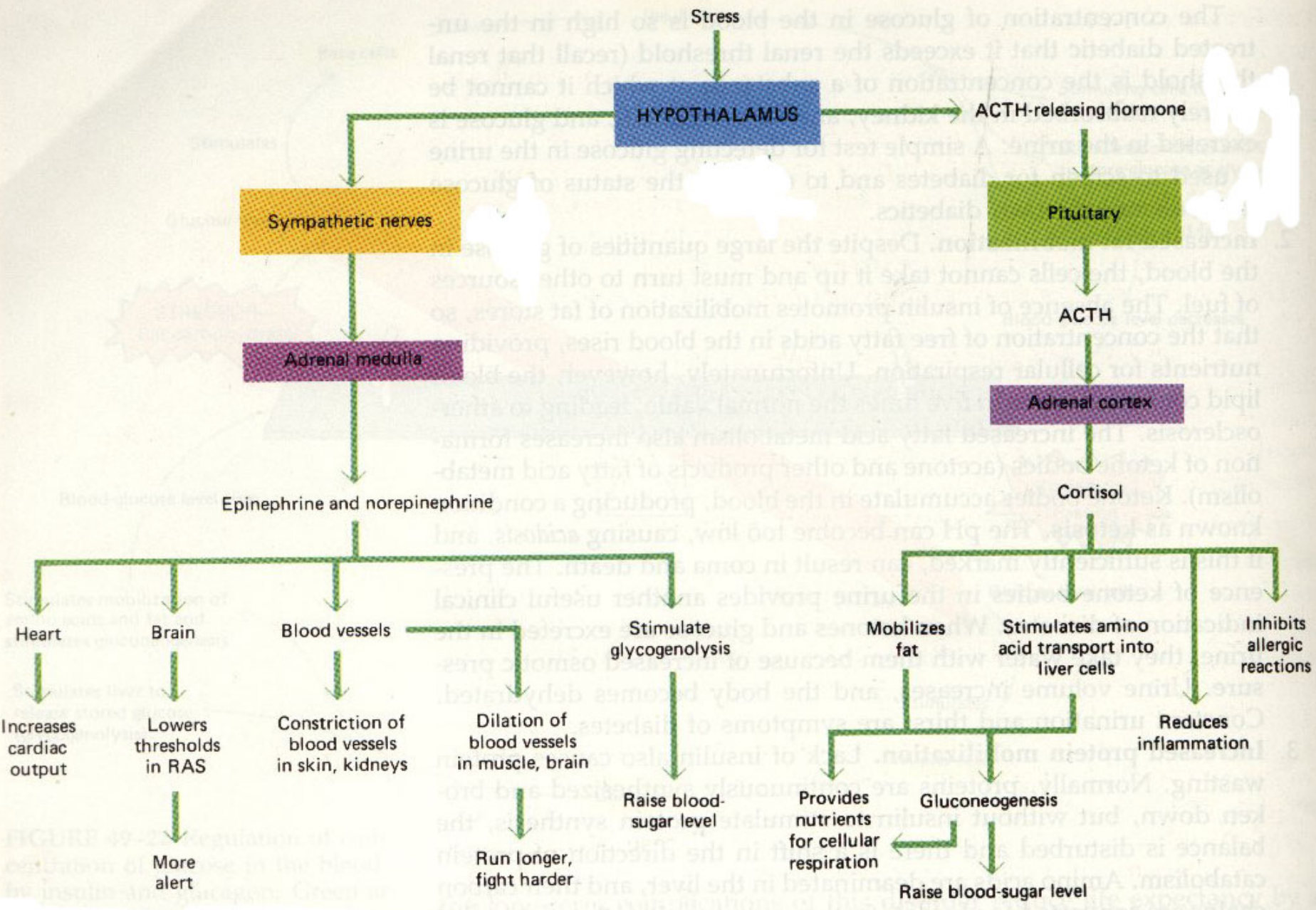
- Alarm reaction- mediates mainly by norepinephrine from the sympathetic nervous system and epinephrine from the adrenal medulla
 - they prepare the body to take action
 - causes a consumption of glycogen
 - aldosterone level rise to promote sodium and water conservation, which helps to offset possible losses by sweating and bleeding
 - angiotensin levels rise to raise the blood pressure

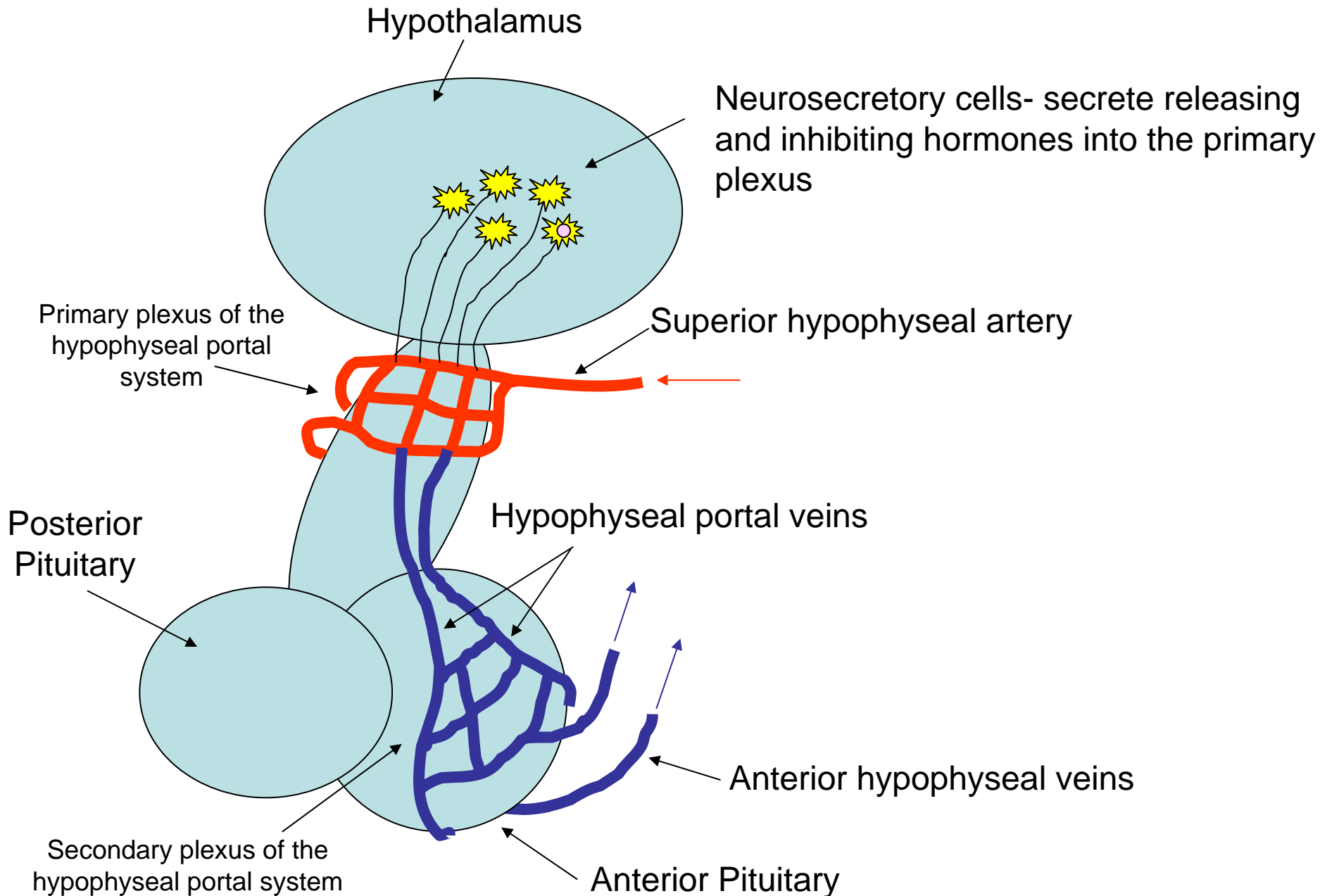
Stress

- Stage of Resistance- occurs when the bodies glycogen reserves are exhausted and the body begins to provide alternative fuels for metabolism.
- This stage is dominated by cortisol which promotes the break down of fat and protein for gluconeogenesis.
- It also inhibits protein synthesis, leaving the free amino acids available for gluconeogenesis
 - The immune system is depressed with long term cortisol exposure due to its heavy dependency of protein synthesis of antibodies and other products
 - Wounds heal poorly
 - gastric secretions increase leading to ulcers
 - depresses the secretion of sex hormones
- This stage leaves the body more susceptible to disease and cancer

Stress

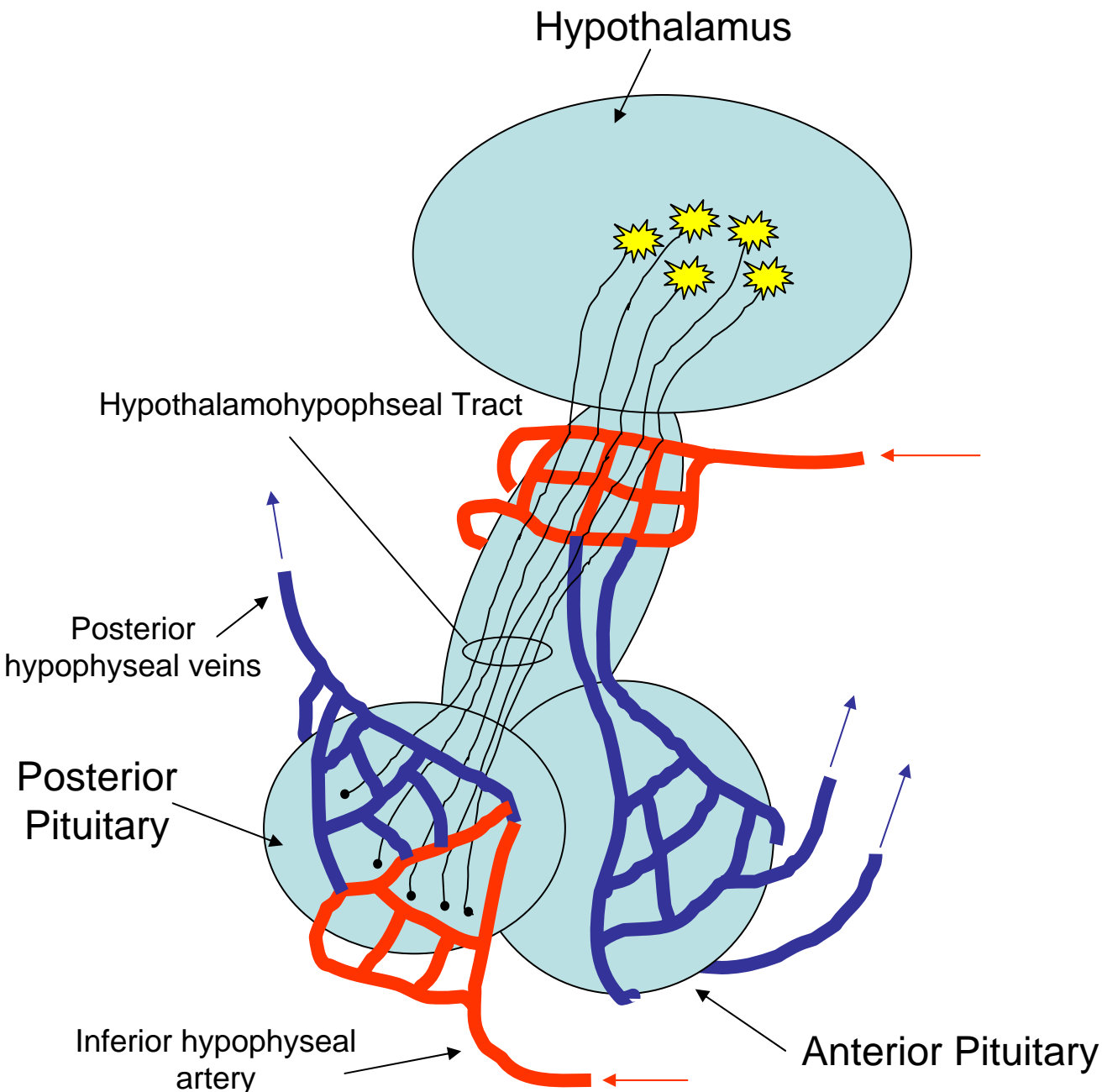
- Stage of exhaustion- when the fat stores are depleted and the body turns to protein for fuel
- Leads to a progressive weakening and wasting away of muscle
- eventually the adrenal cortex stops producing glucocorticoids, making fuel homeostasis impossible
- At last, the effects of aldosterone begins to be detrimental to the body
 - increase retention of sodium and water creates hypertension
 - elimination of potassium and hydrogen causes hypokalemia and alkalosis resulting in nervous and muscular system dysfunction
 - death usually results from heart failure, kidney failure, or overwhelming infection





Anterior Pituitary

- Tropic (trop=turn on) hormones- hormones that influence another endocrine gland
- Ant pit hormones are stimulated by releasing hormones and suppressed by inhibiting hormones from the hypothalamus.
- Hypo hormones reach the ant pit via the portal system

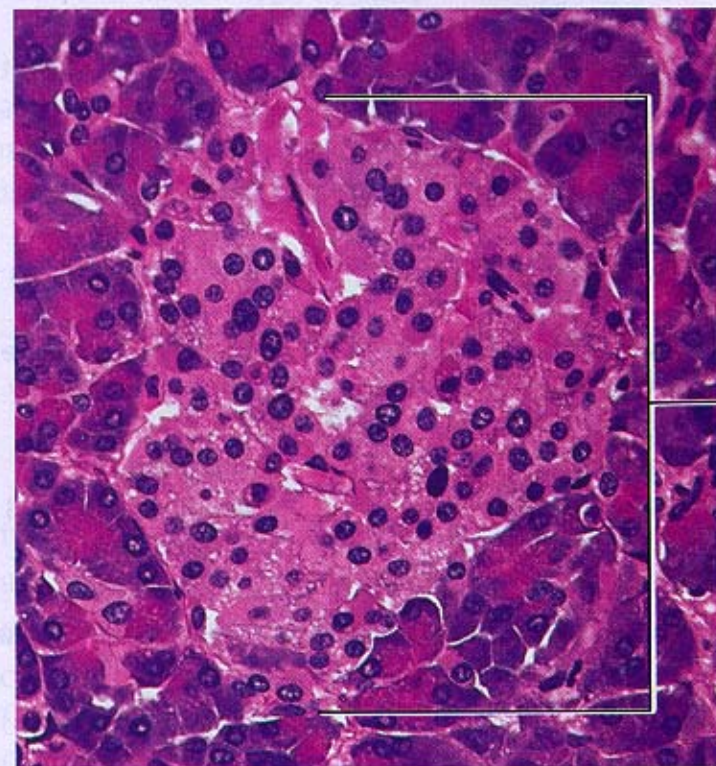
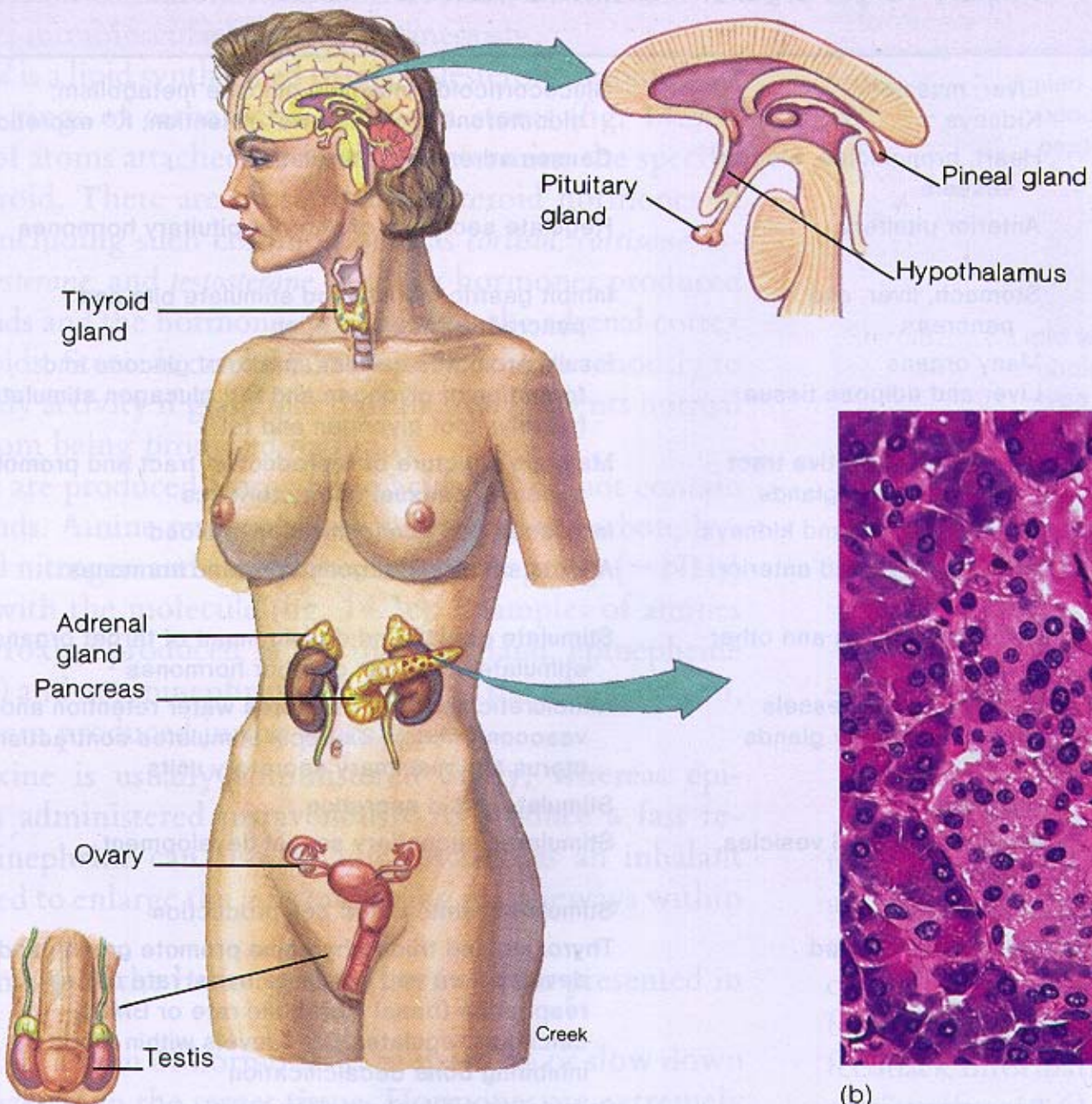


Nervous System and Endocrine System

- The Nervous System and the Endocrine System Coordinate Functions of the Body Systems
 - The nervous system controls homeostasis through nerve impulses that trigger the release of neurotransmitters whose effect results in either the excitation or inhibition of other neurons, muscle fibers, or gland cells.
 - The endocrine system releases hormones into the bloodstream which travels to the target organ where it alters the physiological activity of the cells.

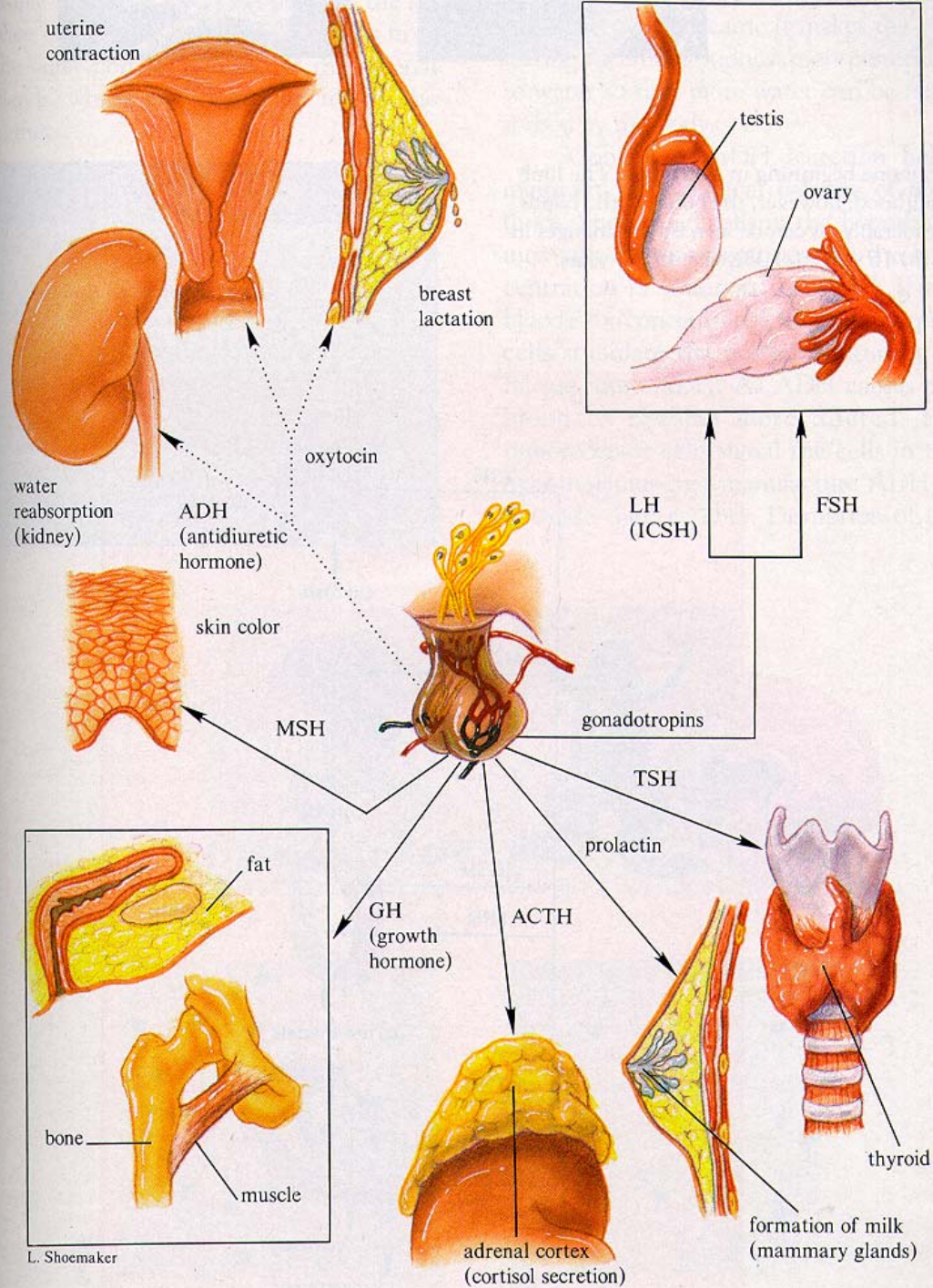
Exhibit 13.2 Chemical Classes of Hormones, Examples, and Sites of Production

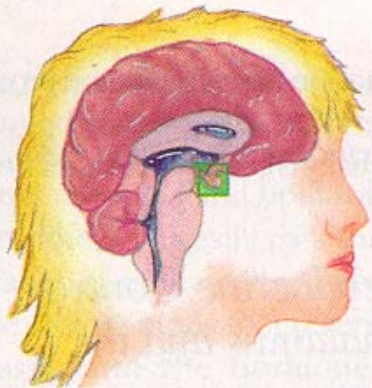
CHEMICAL CLASS	EXAMPLES	WHERE PRODUCED
1. Lipid derivatives		
Steroid hormones	Aldosterone, cortisol, and androgens (male sex hormones)	Adrenal cortex
	Testosterone	Testes
	Estrogens and progesterone (female sex hormones)	Ovaries
Eicosanoids	Prostaglandins and leukotrienes	All cells except red blood cells
2. Amino acid derivatives		
	T ₃ and T ₄ (thyroid hormones)	Thyroid (follicular cells)
	Epinephrine and norepinephrine	Adrenal medulla
3. Peptides and proteins		
	All hypothalamic releasing and inhibiting hormones	Hypothalamus
	Oxytocin, antidiuretic hormone	Hypothalamus
	All anterior pituitary gland hormones	Anterior pituitary gland
	Insulin, glucagon	Pancreas



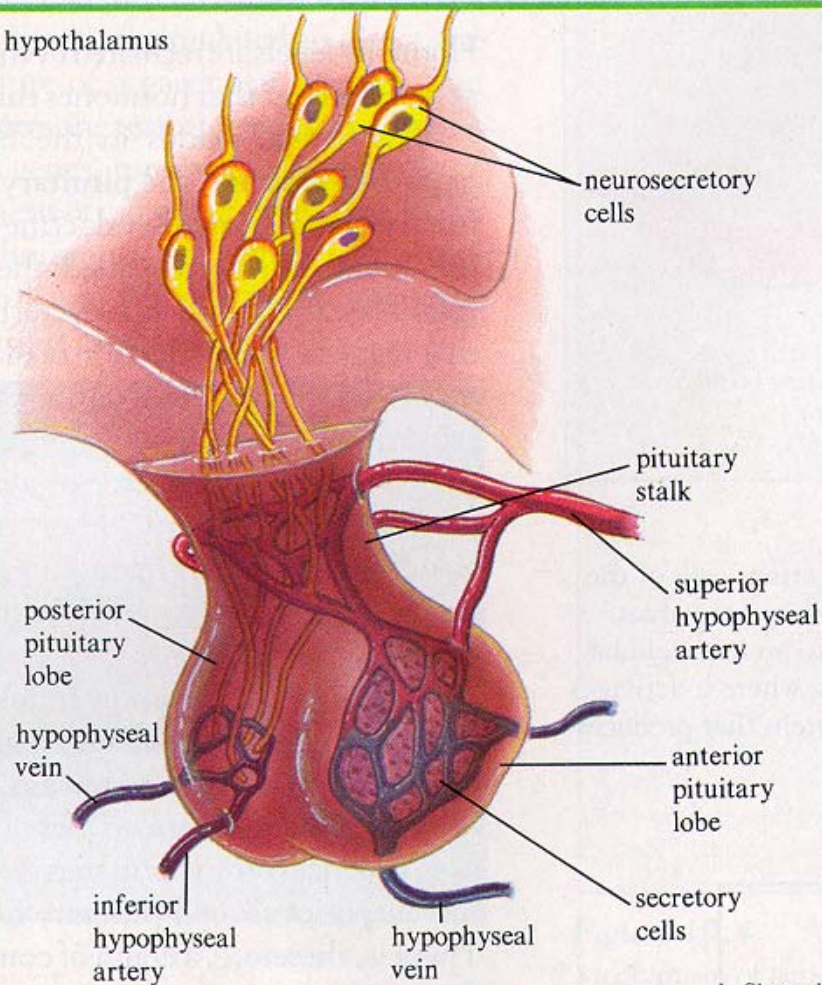
Pancreatic islet

(b)

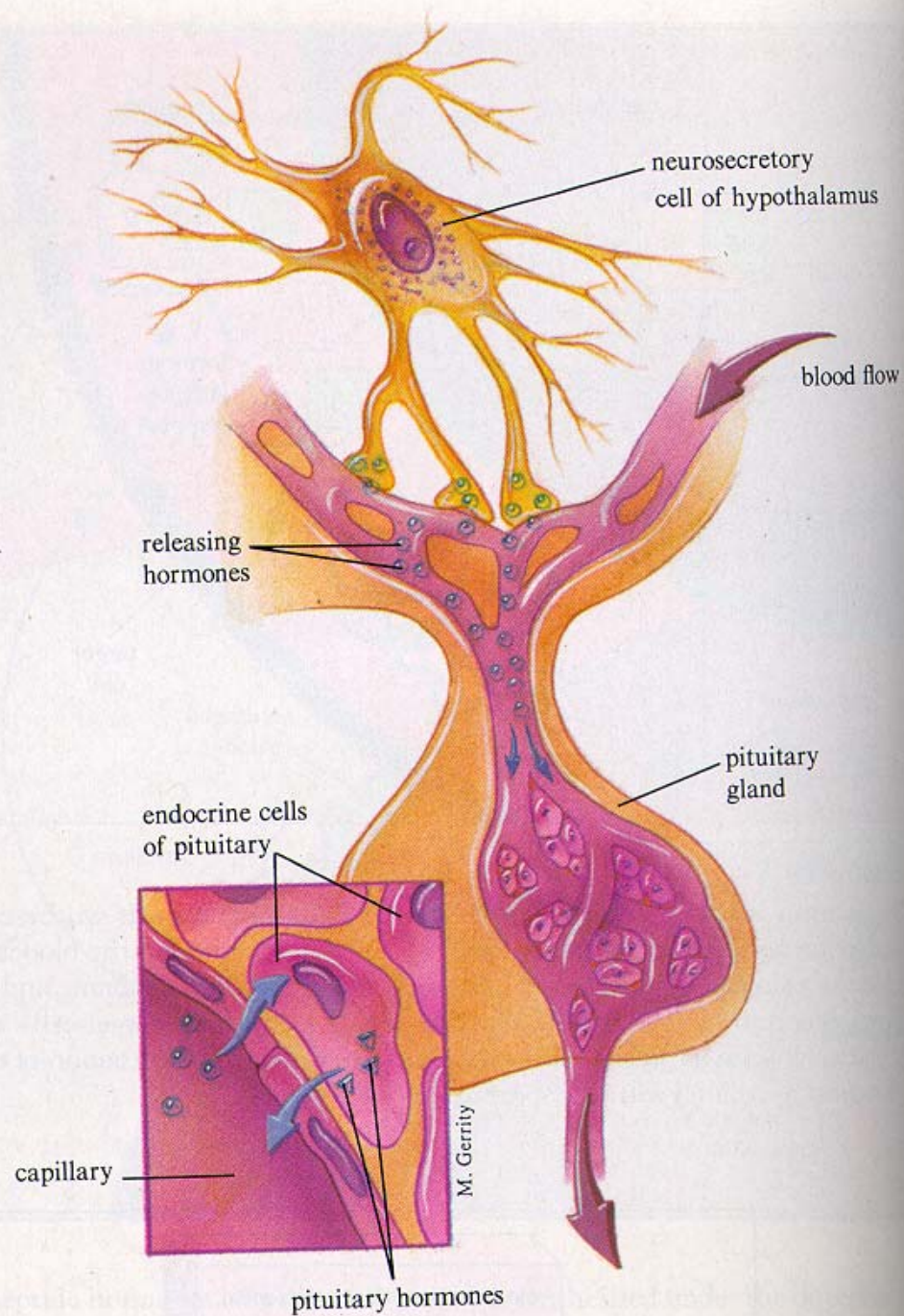




hypothalamus

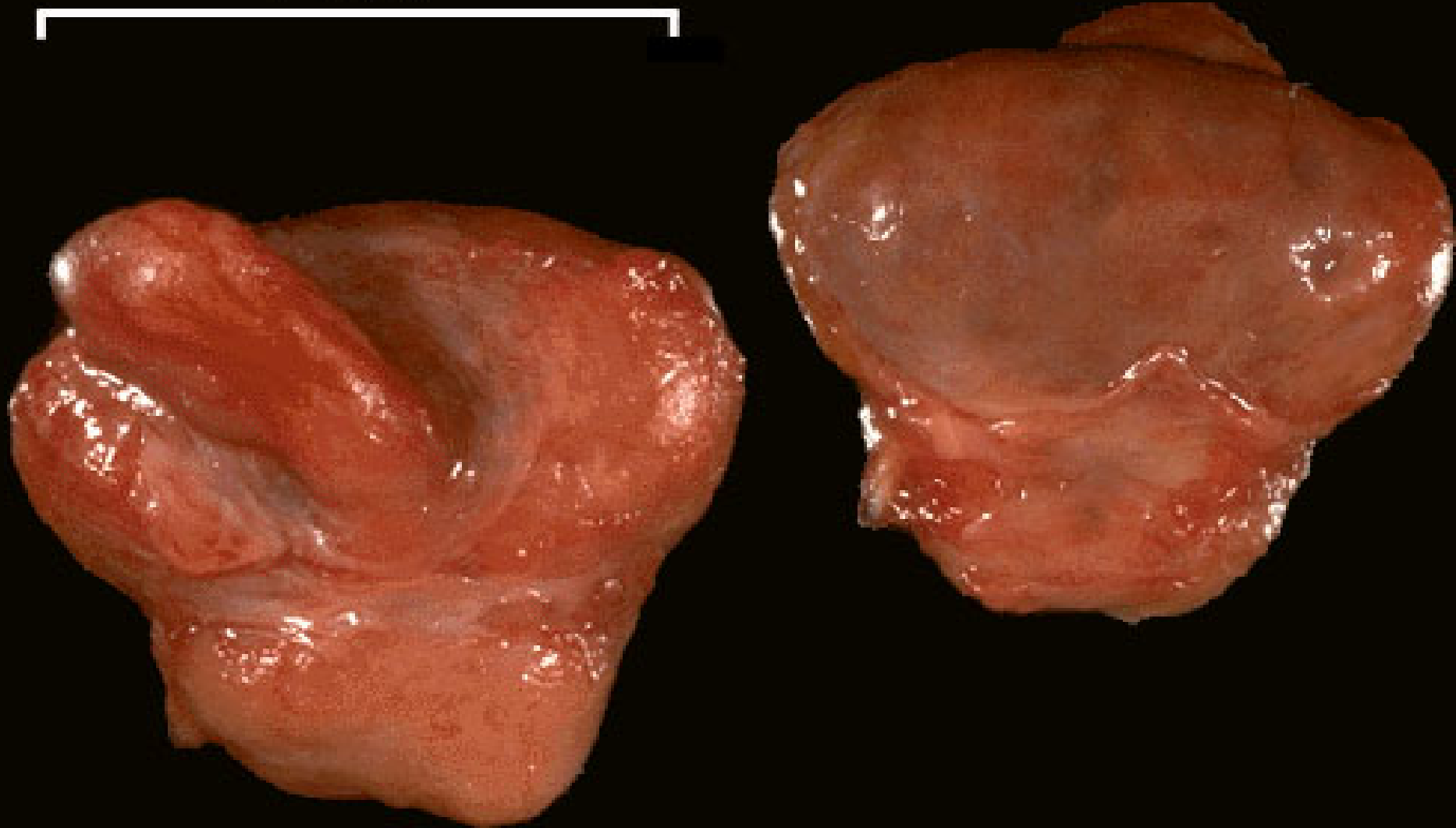


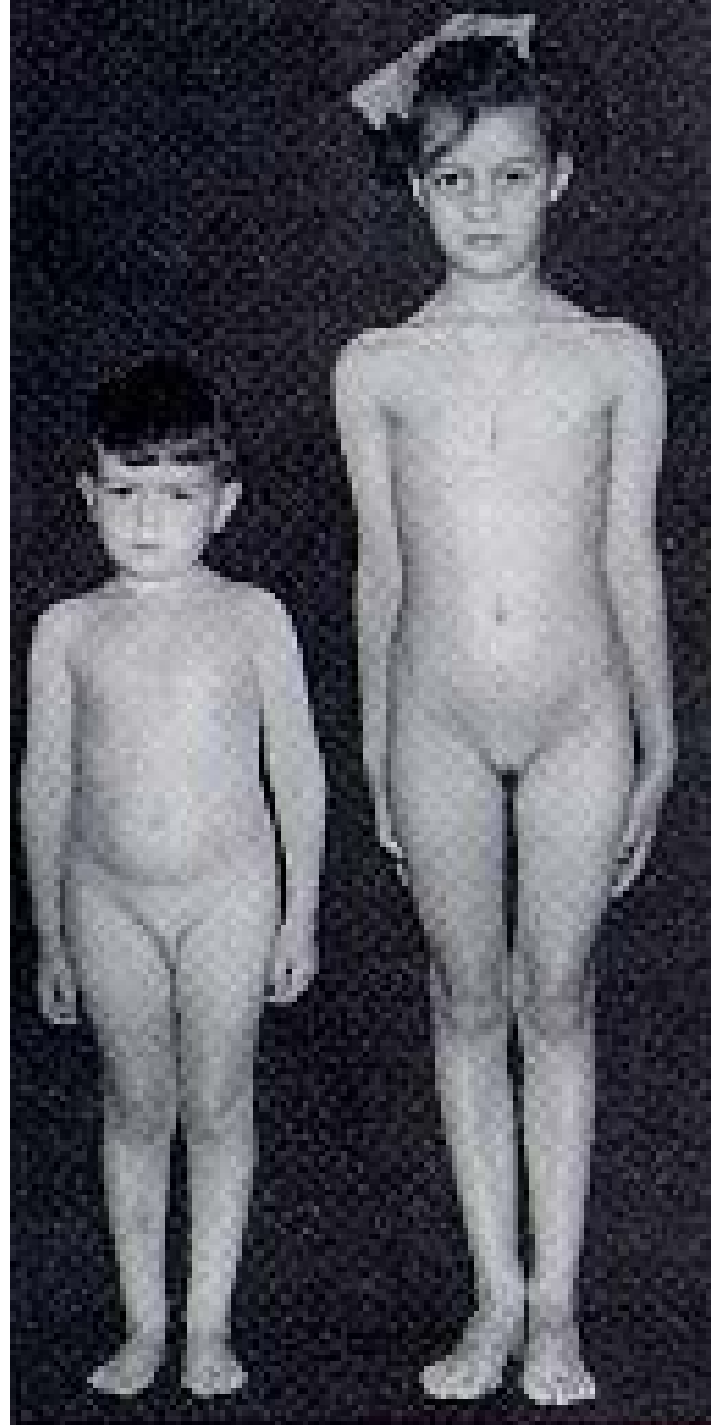
L. Shoemaker



The normal gross appearance of the **pituitary gland** removed from the sella turcica is shown here. The larger portion, the anterior pituitary (adenohypophysis), is toward the top. The image at the left shows the superior aspect of the pituitary with the stalk coming from the hypothalamus entering it. The inferior aspect of the pituitary is shown at the right. The posterior pituitary (neurohypophysis) is the smaller portion at the bottom.

1 cm







(a)



(b)



(c)



(d)

Larynx

Thyroid gland

Isthmus

(a)

Anterior view

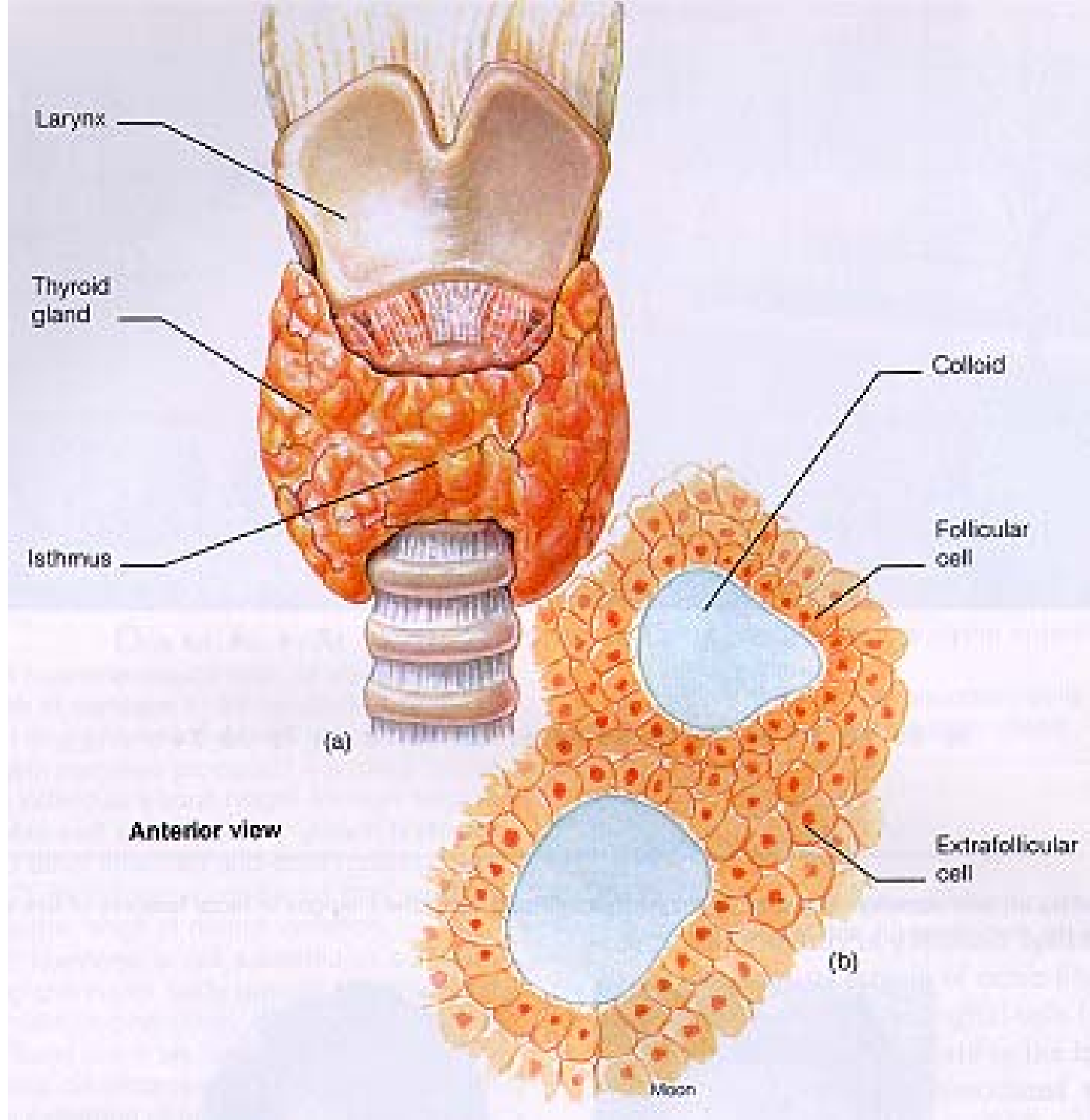
Colloid

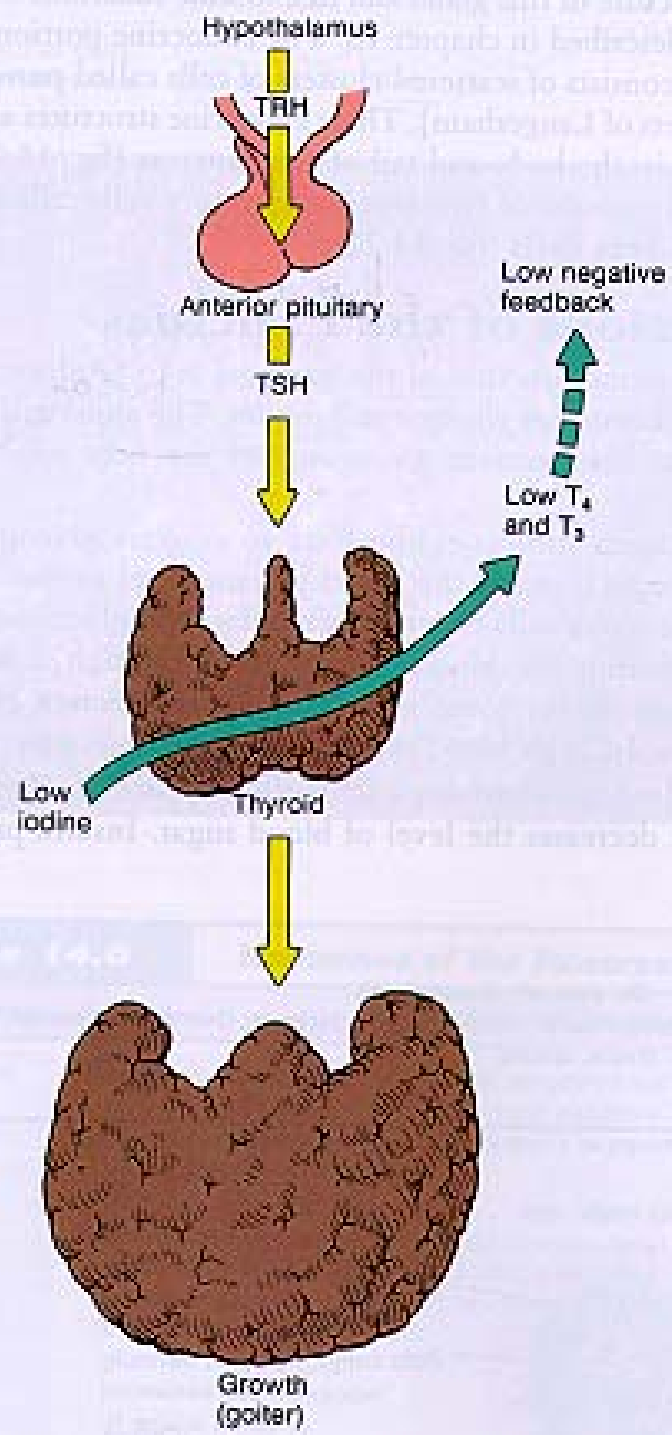
Follicular cell

Extrafollicular cell

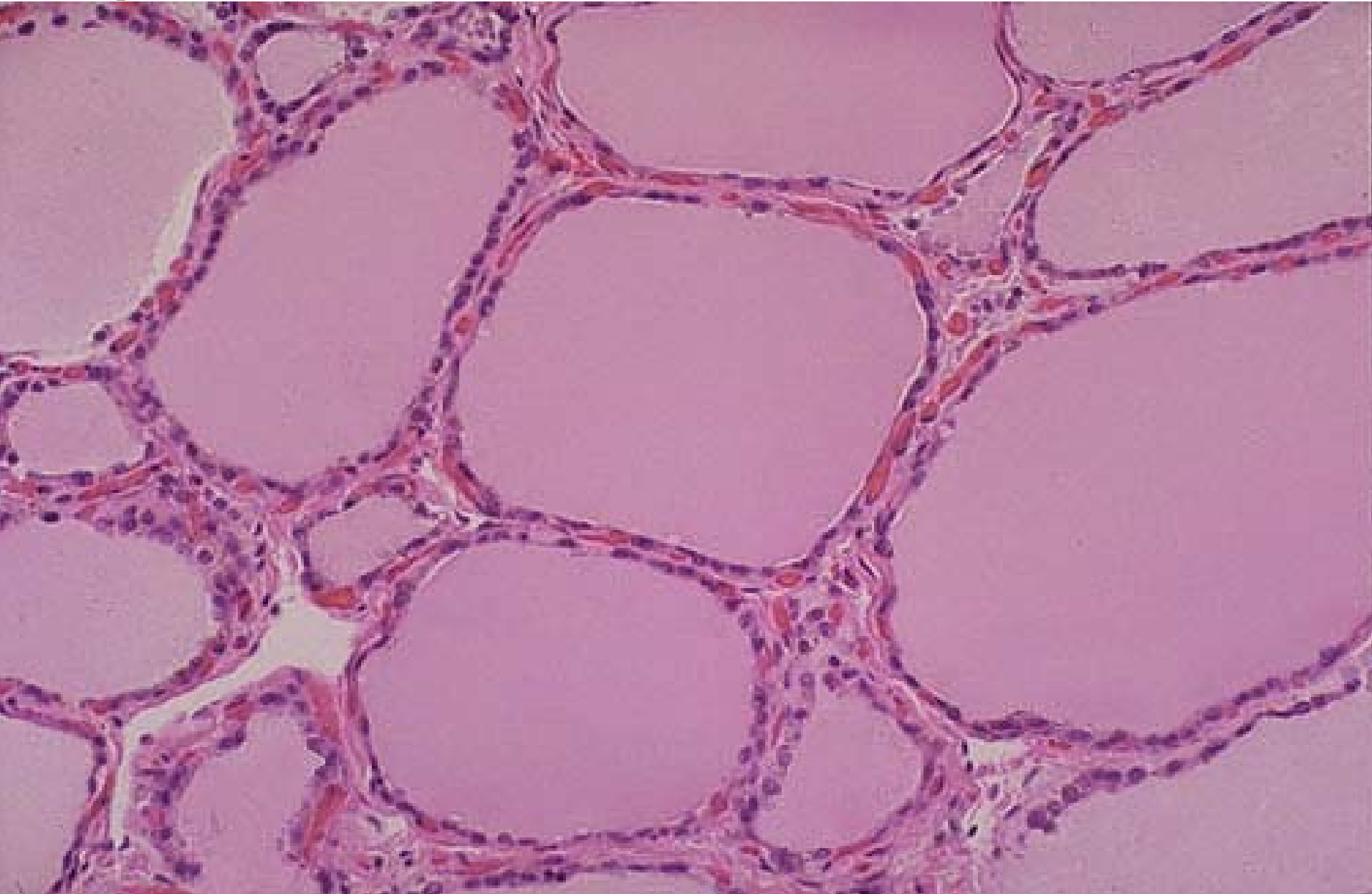
(b)

Moore





Normal thyroid seen microscopically consists of follicles lined by a an epithelium and filled with colloid. The follicles vary somewhat in size. The interstitium, which may contain "C" cells, is not prominent.



This normal thyroid follicle is lined by a cuboidal follicular epithelium with cells that can add or subtract colloid depending upon the degree of stimulation from TSH (thyroid stimulating hormone) released by the pituitary gland. As in all endocrine glands, the interstitium has a rich vascular supply into which hormone is secreted.



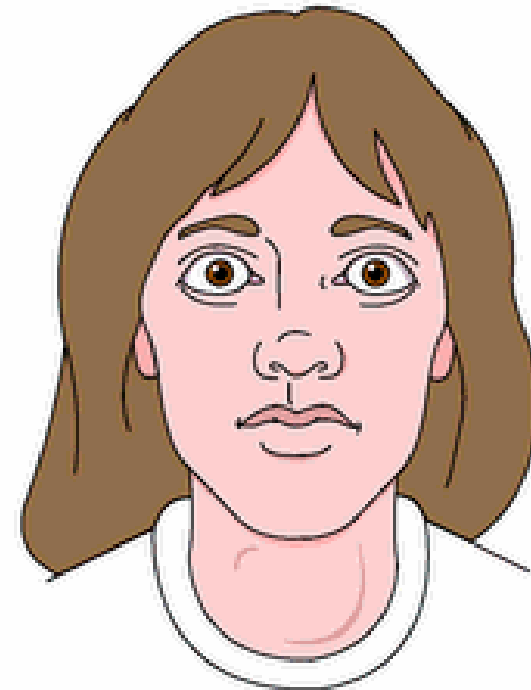
Hyperthyroidism- The most common cause of hyperthyroidism is *Graves' disease*. This occurs when the body's immune system overstimulates the thyroid.

Common symptoms of hyperthyroidism are:

- **Jitteriness, shaking, increased nervousness, irritability**
- **Rapid heart beat or palpitations**
- **Feeling hot**
- **Weight loss**
- **Fatigue, feeling exhausted**
- **More frequent bowel movements**
- **Shorter or lighter menstrual periods**

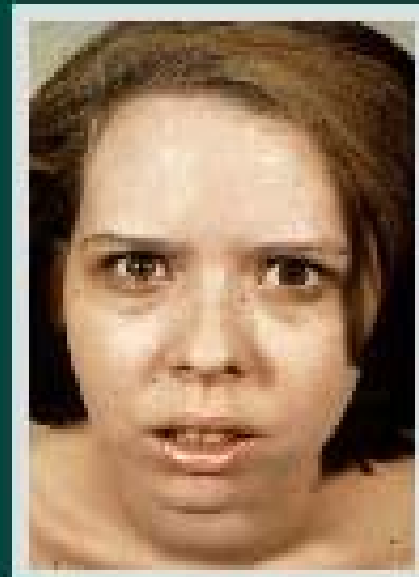
In addition to symptoms of hyperthyroidism, some patients with Graves' disease develop eye symptoms such as a stare, eye irritation, bulging of the eyes and, occasionally, double vision **or** loss of vision.

Involvement of the eyes is called **Graves' Ophthalmopathy**



Graves' Disease

- ◆ Goiter
- ◆ Hyperthyroidism
- ◆ Exophthalmos
- ◆ Localized myxedema
- ◆ Thyroid acropachy
- ◆ Thyroid stimulating immunoglobulins

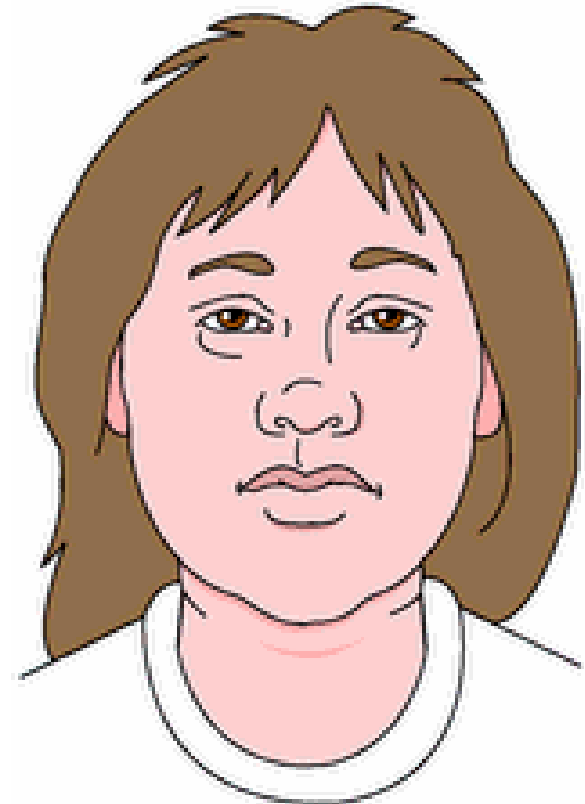


HYPOTHYROIDISM (Underactive thyroid)

The most common cause of hypothyroidism is *Hashimoto's thyroiditis*. In this condition, the body's immune system mistakenly attacks the thyroid gland.

Common symptoms of hypothyroidism are:

- Fatigue or lack of energy
- Weight gain
- Feeling cold
- Dry skin and hair
- Heavy menstrual periods
- Constipation
- Slowed thinking



Parathyroid hyperplasia is shown here. Three and one-half glands have been removed (only half the gland at the lower left is present). Parathyroid hyperplasia is the second most common form of primary hyperparathyroidism, with parathyroid carcinoma the least common form.



